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ROLE OF SOMATOTROPHIC HORMONE IN THE PRODUCTION OF MALIGNANT NEPHROSCLEROSIS, PERIARTERITIS NODOSA, AND HYPERTENSIVE DISEASE

BY

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[WITH SPECIAL PLATE]

During exposure to stress large amounts of corticotrophic and corticoid hormones are discharged into the blood as part of the general-adaptation syndrome (Selye, 1936, 1937, 1950b). Hence the question arose whether, during adaptation to stress, intoxication with endogenous corticoids could predispose the organism to the development of disease.

It was found, by experimentation on animals, that malignant nephrosclerosis, periarteritis nodosa, as well as morphological changes reminiscent of the hypertensive and rheumatic diseases can be produced by mineralocorticoid substances such as desoxycorticosterone acetate (D.C.A.) (Selye and Pentz, 1943) or desoxocortisone (Reichstein's "compound S") (Selye, 1950a).

An impure corticotrophic lyophilized anterior pituitary (L.A.P.) preparation also proved to cause hypertension, with lesions in the cardiovascular and connective tissues quite similar to those seen in the so-called "collagen diseases" (Selye, 1944, 1946).

The similarity between the actions of D.C.A. and L.A.P. became even more evident when it was found that both these hormone preparations predispose to the production of experimental arthritis (Selye, 1949a) and to anaphylactoid reactions (Selye, 1949b). It was therefore tentatively assumed that L.A.P. may act by virtue of its corticotrophic effect, perhaps by stimulating the production of mineralo-corticoids.

Subsequent observations revealed that L.A.P. does not elicit the above-mentioned cardiovascular and renal changes in adrenalectomized rats maintained on cortical extracts. Thus it became extremely probable that the effect of the pituitary preparation is actually mediated through the adrenal cortex (Hall *et al.*, 1946; Ingle, 1950).

However, later, when adequate amounts of highly purified A.C.T.H. became available, it was noted that even the highest tolerable doses of this hormone fail to reproduce the above-mentioned actions of L.A.P. In particular, A.C.T.H. causes no nephrosclerosis; it exerts only irregular effects upon the blood pressure, and, far from eliciting "collagen disease" and predisposing to arthritis or aliergy, it actually inhibits their development, both in experimental animals and in man. Crystalline pure gluco-corticoids—for example, cortisone—act essentially like A.C T.H., not like L.A.P. or D.C.A. Therefore we had to assume that A.C.T.H. is predominantly a "gluco-corticotrophic" hormone—that is, one which stimulates the adrenal to produce gluco-corticoids. From the above it became obvious that the active principle in L.A.P. could not be A.C.T.H., but since the second corticotrophin has not yet been identified, it was meanwhile merely designated as the "L.A.P. factor," or "X factor," of the pituitary.

If L.A.P. is administered to rats simultaneously with A.C.T.H. the nephrotoxic actions and cardiovascular damage induced by the former are considerably aggravated (Selye, 1950a). This led us to suppose that perhaps the "L.A.P. factor" so conditions the response of the adrenal cortex to A.C.T.H. that the latter becomes "mineralo-corticotrophic" (Selye, 1950b, 1950c).

It will be recalled that L.A.P.—which is merely a dried anterior pituitary powder—contains all the adrenohypophysial principles and much accompanying nonhormonal protein material. However, the preparation is particularly rich in somatotrophic hormone (S.T.H.), as shown by the fact that it considerably promotes somatic growth, as well as the proliferation of connective and lymphatic tissues. All these actions are shared by electrophoretically pure S.T.H. (Evans *et al.*, 1948; Simpson *et al.*, 1949).

The experiments reported here show that the above-mentioned desoxycorticosterone-like (mineralo-corticoid) actions of the "L.A.P. factor" can be reproduced by electrophoretically pure S.T.H. They also demonstrate that, under suitable experimental conditions, the simultaneous administration of cortisone inhibits these effects of S.T.H., presumably because it depresses A.C.T.H. secretion by the animal's own pituitary.

Materials and Methods

Two series of experiments have been performed in which S.T.H. was administered in conjunction with cortisone. In each instance the changes observed were compared with the norm and with those elicited by cortisone or S.T.H. alone.

As the two experiments were conducted in essentially the same manner they may well be discussed conjointly.

Experimental Animals.—In both experiments female piebald rats weighing 105–140 g. were used exclusively. In

all of them the right kidney was removed on the day preceding the administration of the first injections. The animals received a powdered "Purina Fox Chow" diet and were given 1% NaCl solution instead of drinking-water. The unilateral nephrectomy was done and the NaCl supplement was administered because these factors had previously been shown to increase sensitivity to the nephrosclerotic action of L.A.P. (Selye, 1950b). The first experiment was terminated after 27 days, the second after 17 days. The animals were killed by exsanguination and the organs immediately removed for weighing and histological examination.

Preparation and Administration of the S.T.H. Solution.—In the first experiment two S.T.H. preparations were employed—one supplied by the Armour Company (lot No. R20-5), the other by Professor C. H. Li, of Berkeley, California (lot No. L1643M). Professor Li's preparation proved to be a homogeneous material as judged by electrophoresis studies. Biological assays did not show L.H., F.S.H., lactogenic, or A.C.T.H. contamination, but they revealed a trace of thyrotrophic activity. The Armour preparation has not been subjected to electrophoretic analysis; however, judged by our own studies, it was also essentially free of contaminating pituitary principles. Both S.T.H. preparations were dissolved in 1% NaCl in such a manner that each individual dose was contained in 0.2 ml. of the solvent. Li's preparation was given at the dose of 3 mg., Armour's at the dose of 6 mg. a day, divided into three injections, given once every eight hours throughout the day and night.

Preparation and Administration of the Cortisone Solution.—In both experiments cortisone was used in the form of cortisone acetate micro-crystals, as prepared by Merck and Co. (25 mg. per ml.), suspended in saline solution with added suspending agents. In the first experiment 5 mg. was injected subcutaneously once daily during the first seven days and 2.5 mg. daily during the rest of the experiment. In the second experiment 5 mg. a day was given during the first seven days and 10 mg. a day during the rest of the period of observation.

Measurement of Water Turnover.—In both experimental series only the water intake was measured daily, as the accurate collection of urine is technically difficult in the rat. In the tables the corresponding figures represent the mean values during the 10 last days of observation.

Measurement of the Blood Pressure.—The blood pressures were determined by the tail-cuff method, under light ether anaesthesia, once a week. The values so obtained are intermediate between systolic and diastolic pressures, but closer to the former. The figures given in the tables represent the means of the last blood-pressure measurements in all instances.

Production of Experimental Arthritis.—In both series an experimental arthritis was produced on the eighth day of the experiment by a modification of the "topical irritation arthritis" test. While in earlier studies a formalin solution was employed to cause local irritation (Selye, 1949c), we have now employed a 10% suspension of mustard powder, of which 0.1 ml. is injected under the plantar aponeurosis in the metatarsal region of the left hind leg. The degree of swelling and inflammatory granuloma formation is expressed in a scale from 0 to +++, and the mean values are listed in the tables. The severity of the lesion was estimated three days after the injection of the mustard powder.

Results of First Experimental Series

Changes in Body and Organ Weights

The distribution of the animals into the six groups of this experimental arrangement, as well as the body and organ weights, is summarized in Table I, together with the standard errors for each figure. In order to facilitate the evaluation of the changes observed, the weights of all organs have been expressed both in mg. (with the standard error) and in mg./100 g. of body weight. This was deemed advisable because the final body weight of the rats in the various groups of this experiment were very different, owing to the anabolic effect of S.T.H. and the catabolic action of cortisone.

In accord with expectations, S.T.H. (groups II and V) greatly increased *somatic growth*, while cortisone actually diminished body weight below the initial value (group III). It is also evident that the catabolic effect of cortisone has been abolished by simultaneous treatment with either of the two S.T.H. preparations (groups IV and VI). Indeed, the animals receiving S.T.H. plus cortisone had a higher final body weight than the untreated controls, although they were not as heavy as the rats receiving S.T.H. alone. We may conclude that there is a direct antagonism between the anabolic effect of S.T.H. and the catabolic action of cortisone. These observations suggest that the individual variability in the requirements for cortisone in patients, in whom the hormone is given for therapeutic reasons, may likewise be largely conditioned by the availability of S.T.H. within the organism.

The weight of the *heart* (expressed either in absolute terms or as a percentage of the body weight) was greatest in the animals receiving S.T.H. (Li) plus cortisone. There was also some cardiac enlargement in the rats receiving

TABLE I.—*Summary of Organ Weights in the First Experiment**

Group:	I Normal Controls	II S.T.H. (Li)	III Cortisone	IV S.T.H. (Li) + Cortisone	V S.T.H. (Armour)	VI S.T.H. (Armour) + Cortisone
No. of rats per group	6	3	6	3†	3	3
Initial body weight in g.	113	116	114	113	113	113
Final body weight in g.	147±5·8	175±20	109±6	153	181±25	166±6·3
Heart in mg.	532±23	864±49	512±32	1,018	734±146	667±46
Heart in mg./100 g.	362	494	512	665	405	402
Kidney in mg.	794±123	1,460±68	673±117	2,076	1,187±283	983±73
Kidney in mg./100 g.	540	834	673	1,357	656	592
Liver in mg.	6,332±131	10,879±36	4,596±507	11,282	8,633±509	7,634±116
Liver in mg./100 g.	4,307	6,216	4,596	7,374	4,770	4,599
Adrenals in mg.	37±1·8	57±0·07	11±1·6	50	49±8·2	20±0·09
Adrenals in mg./100 g.	25	33	11	33	27	12
Thymus in mg.	192±18	81±61	33±3·4	18	163±60	59±20
Thymus in mg./100 g.	131	46	33	12	90	35
Spleen in mg.	745±47	1,090±60	433±42	1,154	879±146	810±94
Spleen in mg./100 g.	507	623	433	754	486	488

* In the text we did not evaluate the statistical significance of each figure, especially since the interested reader can readily do so with the aid of the standard errors given here. It should be emphasized, however, that many of the inferences drawn in the text are based on a conjoint consideration of the data given in the four tables and of histological observations which do not lend themselves to statistical evaluation.

† Two of the rats in this group succumbed several days before the termination of the experiment. Hence, their organ weights were not pooled with the rest and thus standard errors cannot be given in this column. These animals died with severe nephrosclerosis and myocarditis, without signs of adrenal atrophy. This fact speaks (even more definitely than organ weights would) in favour of our conclusion that under these conditions when cortisone fails to cause adrenal involution it aggravates the nephrotoxic and cardiotoxic actions of S.T.H.

S.T.H. (Li) or S.T.H. (Armour) alone. However, the cardiac enlargement caused by S.T.H. (Armour) was not further increased by simultaneous cortisone administration. Indeed, the animals given S.T.H. (Armour) plus cortisone had a slightly smaller heart weight than those receiving S.T.H. (Armour) alone. An attempt at a theoretical evaluation of these differences in the actions of the two S.T.H. preparations is made later, in the section entitled "Discussion." However, for the sake of clarity, it may be mentioned here that in this (and in all other pertinent experiments performed in our Institute) cortisone tended to aggravate the cardiac, vascular, and renal damage caused by S.T.H. overdosage whenever it failed to cause marked adrenocortical involution; conversely, cortisone actually inhibited these S.T.H. effects under experimental circumstances which permitted it to induce the usual "compensatory atrophy" of the adrenal cortex.

The weight of the *kidney* (both in absolute terms and when expressed as a percentage of body weight) was largest in the animals receiving cortisone and S.T.H. (Li) simultaneously. Both S.T.H. preparations, when given alone, also caused a marked, absolute, and relative renal enlargement. However, the increase in kidney weight induced by S.T.H. (Armour) was actually diminished by simultaneous cortisone treatment.

Both S.T.H. preparations caused a pronounced increase in the weight of the *liver*. This was further accentuated by simultaneous cortisone administration in the case of S.T.H. (Li), but was diminished by this same steroid in the animals receiving S.T.H. (Armour). The fact that cortisone augmented the hepatic weight increment caused by S.T.H. (Li) is all the more significant since in these same animals the somatic weight increase elicited by S.T.H. (Li) was actually diminished by cortisone. Apparently, under these conditions, there is a dissociation between the general anti-anabolic effect of cortisone (as revealed by the somatic weight) and its action upon the growth of renal and hepatic tissue.

It is relevant to mention that in certain species, such as the rabbit, cortisone itself causes a pronounced increase both in the absolute and in the relative weight of the liver (Timiras, unpublished). The reason for this species difference in the responsiveness of the liver to cortisone has not yet been elucidated.

The *adrenals* underwent pronounced compensatory atrophy in the rats treated either with cortisone alone or with cortisone plus S.T.H. (Armour). Conversely, in the rats receiving S.T.H. (Li) in conjunction with cortisone the adrenal weight was far above that of the uninjected controls. When expressed as a percentage of the body weight the adrenal weight in the animals receiving S.T.H. (Li) plus cortisone was almost exactly the same as in those receiving this S.T.H. preparation alone. This implies that, under the conditions of this experiment, cortisone failed to inhibit the adrenal-stimulating effect of S.T.H. In sharp contrast to the above-mentioned findings, the rats treated with S.T.H. (Armour) showed a much less pronounced adrenal enlargement; indeed, this was almost negligible when the adrenal weight was expressed as a percentage of the body weight. Furthermore, in the animals treated with S.T.H. (Armour) simultaneous injection of cortisone caused considerable adrenal atrophy both in absolute and in relative terms.

The *thymus* of all four groups receiving cortisone, alone or in combination with one of the S.T.H. preparations, was almost maximally involuted; hence the apparent differences between these groups do not lend themselves well to an analysis of the underlying mechanism. Yet it is noteworthy that simultaneous treatment with S.T.H. (Li) tended to accentuate, and S.T.H. (Armour) to counteract, the thymus involution normally caused by cortisone alone. Although the figures leave much doubt about the significance of this antagonism they clearly show at least the absence of a synergism of cortisone with S.T.H. (Armour) such as is noted with S.T.H. (Li). This (like the adrenal changes) suggests that some A.C.T.H.-like effect accompanied the administration of S.T.H. (Li) under these conditions.

The *spleen* was smallest in the animals treated with cortisone alone, while it was much enlarged after S.T.H. (Li). S.T.H. (Armour) caused a lesser splenic enlargement, which failed to be manifest if the organ weight was expressed per 100 g. of body weight. It is particularly noteworthy that, although the somatic weight increase caused by either S.T.H. preparation was so considerably inhibited by simultaneous cortisone treatment, the splenic enlargement was not significantly affected by this steroid. This fact (as well as the above-mentioned observations concerning cardiac, renal, and hepatic weights) further illustrates the lack of proportionality between somatic anabolism in general and the growth of certain organs in rats treated with S.T.H. plus cortisone. Apparently the cardiotrophic, renotrophic, hepatotrophic, and splenotrophic actions of S.T.H. are much less readily counteracted (and may even be increased) by cortisone than is its general somatotrophic action.

Clinical and Histological Observations

Only some of the clinical and histological observations can be summarized in the form of a table (see Table II). These, as well as other findings, are discussed in more detail below.

TABLE II.—*Summary of Some Clinical and Histological Observations in the First Experiment*

Group:	I Normal Controls	II S.T.H. (Li)	III Cortisone	IV S.T.H. (Li) + Cortisone	V S.T.H. (Armour)	VI S.T.H. (Armour) + Cortisone
Myocarditis	0	++	0	++	+	0
Nephritis + nephrosclerosis	0	++	0	+++	+	0
Pancreatic periarteritis	0	Trace	0	++	Trace	0
Water intake in ml. ..	56±2	196±8·2	39±0·36	166±23	104±7·8	64±2
Blood pressure in mm. Hg	128±7·6	177±53	153±11·5	142	153±14	149±14
Arthritis test	++	+++	0	+	+++	+

It may be stated at the onset that the changes observed in the heart, kidney, and the pancreatic vessels were essentially similar to those previously observed after treatment with D.C.A. or L.A.P. (Selye, 1950b). In the table these are listed under the headings "myocarditis," "nephritis plus nephrosclerosis," and "pancreatic periarteritis" respectively. Their severity is expressed in a scale of 0 to +++, which represents the mean change in each group. The designation "trace" is employed when the mean reading falls below one +.

In the *hearts* of the rats treated with S.T.H. (Li) we found the usual granulomatous nodules, situated either between the muscle fibres or underneath the endocardium, rarely in the subepicardial layer. These nodules consist of proliferating connective tissue cells, many of which are in various phases of mitotic division.

Some of these elements develop several irregular processes and thus lose their normal spindle shape. Their cytoplasm often exhibits a diffuse basophilia. The endothelial cells which line the capillaries and small arterioles tend to become hypertrophic and in many places protrude deeply into the lumina of the vessels, thus resembling a cuboidal or cylindrical epithelium. These granulomas are frequently invaded by lymphocytes, plasma cells, and macrophages, and less commonly by a few polymorphonuclear leucocytes and eosinophils. They often also contain polymorphonuclear giant cells, which appear to form either by confluence of endothelial cells in the capillaries or by division of the nuclei (without concomitant division of the cytoplasm) in proliferating connective-tissue cells. Between the cells are masses of more or less homogeneous eosinophilic "hyalin" material. Not infrequently these nodules develop around small arterioles which undergo changes typical of periarteritis nodosa. When such nodules develop underneath the mural endocardium or on the valves they may ulcerate, and then fibrin is deposited on the denuded surface. This fibrin gradually becomes organized by invading connective-tissue strands and vessels. There is a striking similarity between these myocardial changes and those observed in acute rheumatic fever, lupus erythematosus, and Libman–Sacks disease (Plate, Fig. 7).

The above-mentioned cardiac changes were particularly severe in the rats receiving S.T.H. (Li) plus cortisone, but almost as marked in those treated with S.T.H. (Li) alone. They were less pronounced in the animals given S.T.H. (Armour) alone, and here they were completely prevented by concurrent treatment with cortisone.

The *kidneys* of the rats treated with S.T.H. (Li) exhibited a typical malignant nephrosclerosis with periarteritis-nodosa-like changes of the small renal arterioles and glomerular hyalinization. All these changes had been previously noted in D.C.A.-treated animals. In nephrons with early stages of the lesion, the glomerulus is merely enlarged and apparently permeable to plasma proteins, since coagulated proteinaceous material is found in the spaces of Bowman's capsules as well as in the convoluted tubules. These coagula form hyaline casts which may completely obliterate the tubular lumina so that above their level the nephrons are greatly distended with urine. At a later stage the glomerulus becomes highly cellular; its endothelium and the visceral lamina of Bowman's capsule undergo marked hypertrophy and hyperplasia, often accompanied by invasion with polymorphonuclear leucocytes. At this time erythrocytes may appear in the lumina of Bowman's capsules and of the tubules. In some kidneys the hyalinization of vessels and glomeruli, in others the proteinuria, haematuria, and inflammatory glomerular changes predominate. Thus we note various intermediate stages between typical malignant nephrosclerosis and a haemorrhagic type of glomerular nephritis. Lymphoid infiltrates are occasionally seen between the tubules.

The connective tissue around the renal pelvis is always very oedematous and infiltrated by inflammatory cells. In some instances a typical pyelonephritis ensued.

All these changes were more pronounced in the rats treated with S.T.H. (Li) than in those given S.T.H. (Armour); cortisone tended to aggravate them in the former and prevented them in the latter case.

The only respect in which the kidneys of S.T.H.-treated rats appeared to differ from those of D.C.A.-intoxicated animals is that the former usually show very pronounced regenerative changes in the tubules and consequently a much greater weight increase than has been noted after D.C.A. This "renotrophic effect" may well be specific of S.T.H. and quite distinct from its nephrotoxic action, as will be seen in the discussion of these findings below.

The rats treated with cortisone alone showed only marked glomerular hyperaemia with the extreme distension of the glomerular capillaries which is quite characteristic and constant in rats treated with this hormone (Selye, 1950b). (Figs. 1–6. All the photomicrographs in the Plate illustrate organ changes observed in the first experiment.)

In the *pancreas*, obvious changes developed only in the vessels, while the acini and the Langerhans islets remained essentially intact. Pronounced periarteritis nodosa was observed in all the animals treated with S.T.H. (Li) plus cortisone, while S.T.H. (Li) alone caused only minor lesions in one of the animals. Thus, in this respect again, cortisone aggravated the tendency of S.T.H. (Li) to produce "collagen disease." On the other hand, S.T.H. (Armour), which also produced periarteritis nodosa in one of the animals, did not exert such an action in any of the rats treated simultaneously with cortisone (Fig. 8). Histological signs of oedema in the pancreatic stroma ran approximately parallel with the degree of vascular lesion in all groups.

It should be mentioned here that macroscopically visible reddish nodules of *periarteritis nodosa in the mesentery* are almost invariably observed when renal damage is produced by D.C.A. or by the "endocrine kidney technique." Such lesions are quite exceptional, however, in rats in which similar renal damage is elicited by L.A.P. The mesenteric periarteritis nodosa caused by D.C.A can be inhibited by simultaneous treatment with cortisone, even in animals in which the renal damage is actually aggravated by the latter hormone (Selye, 1950b). In the present experimental series, mesenteric periarteritis nodosa outside the pancreas was not observed in any of the animals—an observation which is compatible with the view that S.T.H. is the nephrotoxic factor responsible for the L.A.P. effect.

The *liver* revealed marked parenchymatous hyperplasia and hypertrophy in all S.T.H.-treated animals, whether or not they were also given cortisone. The hepatic cells were enlarged, some of them showed mitotic figures, and in general the cytoplasm exhibited a more or less pronounced basophilia. The hepatic stroma occasionally contained infiltrations with lymphoid and myeloid elements.

The *adrenals* of the rats receiving cortisone alone underwent the usual cortical atrophy, while the medulla remained essentially intact. The involution affected all three layers of the cortex, although the glomerulosa was least atrophic. This may be due to the fact that even normally the glomerulosa cells are poorly developed. The reticulo-endothelial phagocytes of the sinusoids were often laden with brownish blood-pigment derivatives.

Under the conditions of this experiment, S.T.H. (Li) caused a pronounced hypertrophy and hyperplasia of the adrenal cortex, often accompanied by lymphatic and myeloid infiltration islets. These same changes had previously been noted in animals treated with L.A.P. (Selye, 1950b). In rats concurrently given S.T.H. (Li) and cortisone the lymphatic infiltration was significantly less pronounced than in those receiving S.T.H. (Li) alone, presumably because of the well-known antilymphatic effect of gluco-corticoids.

The sinusoids of the adrenal cortex were replete with lymphoid cells, especially in the rats receiving S.T.H.

(Li) alone. In some fields the cortical sinusoids contained almost only lymphoid elements so as to give the impression of a lymphatic leukaemia. However, in other organs we did not observe any comparable increase in the intracapillary lymphocyte number.

In the rat, scattered islands of cortical cells are normally found within the substance of the medulla. They resemble the cells of the reticularis. In our S.T.H.-treated rats these "medullary cortical cells" were particularly prominent and enlarged. All these cortical changes were much more pronounced in the rats treated with S.T.H. (Li) than in those given S.T.H. (Armour). Furthermore, simultaneous administration of cortisone failed to prevent the adrenal hypertrophy caused by S.T.H. (Li), while it almost completely abolished that elicited by S.T.H. (Armour) (Figs. 9–11).

The *thymus* showed obvious histological signs of involution, with disintegration of the thymocytes and proliferation of the reticulum in all cortisone-treated animals, but this was least pronounced in those also receiving S.T.H. (Armour).

The *spleen* exhibited a pronounced atrophy of the lymphoid elements in all the animals treated with cortisone alone. This was accompanied by an involution of the splenic megakaryocytes, which were scarce, and even the few that could be found were subnormal in size. Conversely, the rats treated with S.T.H. (Li)—and to a lesser extent those receiving S.T.H. (Armour)—revealed a marked hyperplasia of lymphoid and myeloid elements, especially in the marginal zone of the Malpighian corpuscles. This was accompanied by a pronounced increase in the number of eosinophilic leucocytes within the splenic parenchyma. Normally, sessile eosinophils are extremely rare in the rat spleen. An extraordinarily large number of hyperplastic megakaryocytes was striking in both S.T.H.-treated groups. Simultaneous treatment with cortisone did not significantly alter the response to either of the S.T.H. preparations. However, in all the animals simultaneously treated with cortisone and either of the S.T.H. preparations there was an obvious increase in the storage of brownish blood-pigment derivatives within the splenic macrophages (Fig. 12).

The *water intake* was greatly increased in all the animals treated with S.T.H. (Li) and, to a less extent, in those given S.T.H. (Armour). Simultaneous treatment with cortisone did not significantly alter the increased water turnover of the rats given S.T.H. (Li), but it almost completely abolished the polydypsia and polyuria of those receiving S.T.H. (Armour). Cortisone in itself caused only a slight inhibition of water turnover.

The mean *blood pressure* was highest in the group receiving S.T.H. (Li). Although cortisone in itself also caused some hypertension, the rise in blood pressure was less pronounced in the rats given S.T.H. (Li) plus cortisone. This is noteworthy since the renal changes were more severe in the latter group. The interpretation of this finding must await further observations, especially since the pressor effect of S.T.H. (Armour) did not appear to be significantly influenced by concurrent cortisone treatment.

The *topical irritation arthritis* test showed that both S.T.H. preparations increase the ability of the rat to produce an inflammatory granuloma at the site of irritation, while cortisone prevents it. This agrees with our earlier observations, which revealed that L.A.P. aggravates, while cortisone inhibits, this type of arthritis (Selye, 1949c). The above observation is also compatible with the view that S.T.H. exerts D.C.A.-like actions, since the latter hormone likewise augments the inflammatory response to local irritation in the joint regions. It is especially noteworthy, however, that both S.T.H. preparations greatly diminished the anti-arthritic effect of cortisone. This agrees with our view that the cortisone requirements of patients are also dependent upon endogenous S.T.H. production.

Results of Second Experimental Series

Perhaps the most clear-cut outcome of our first experiment was that, under our experimental conditions, cortisone influenced the effect of S.T.H. (Li) and of S.T.H (Armour) in a different manner. It must be kept in mind, however, that S.T.H. (Li) was administered at the rate of 3 mg., and S.T.H. (Armour) at the rate of 6 mg. a day. The reason for this difference in dosage was merely that we did not have enough of the former preparation.

Our results made it imperative, however, to determine whether cortisone would inhibit the cardiovascular and renal toxicity of S.T.H. (Li) if the latter were given at a higher dose level. Endocrinology furnishes many examples showing that the action of hormones at low dose levels may be diametrically opposite to that at high dose levels. Thus small amounts of testosterone cause testicular atrophy, large amounts hypertrophy; thyroxine stimulates somatic growth at low and inhibits it at high dose levels, etc.

We also had to consider the possibility that the handling of our experimental animals (blood-pressure measurements, topical irritation arthritis test, repeated injections, etc.) stimulated endogenous A.C.T.H. production, which may have overcompensated for the effects of small doses of S.T.H. This would of course likewise interfere with the ability of cortisone to produce compensatory atrophy of the adrenals. Several (unpublished) preliminary experiments had revealed that cortisone prevents the cardiovascular and renal toxicity of S.T.H. only under conditions which permit it to cause adrenocortical involution. For these reasons we decided to refrain from the publication of the first experimental series until we were able to obtain an additional supply of S.T.H. (Li). Recently, in a second experiment, we increased the daily dose both of S.T.H. (Li) and of cortisone. We hoped that under these conditions any incidental endogenous A.C.T.H. secretion would be comparatively less important in proportion to the high S.T.H. and cortisone dosages injected. Unfortunately, we had only enough electrophoretically pure S.T.H. (Li) to continue this experiment for 17 days, but, even so, it became obvious that under these experimental conditions S.T.H. (Li) behaved in the same manner as the S.T.H. (Armour) had in the first series. In other words, under favourable experimental circumstances the toxicity of either of the two S.T.H. preparations is counteracted by cortisone. Hence, the apparent difference between the two somatotrophic extracts must not be ascribed to inherent dissimilarities of their actions, but to the dose level at which they were given.

The exact experimental procedure has already been outlined above in the section "Materials and Methods." The results as regards body weights, organ weights, and clinical and histological changes were so similar to those reported above for S.T.H. (Armour), alone and in combination with cortisone, that it would be redundant to discuss these here in detail. Suffice it to refer to Tables

III and IV, which are constructed in the same manner as the corresponding Tables I and II of the first experiment.

TABLE III.—*Summary of Organ Weights in the Second Experiment*

Group:		I Normal Controls	II S.T.H. (Li)	III Cortisone	IV S.T.H. (Li) +Cortisone
No. of rats per group		6	3	3	6
Initial body weight in g.		125	130	125	130
Final body weight in g.		143±3·8	215±11	103±6·7	167±2·3
Heart	in mg.	521±13	763±6·5	486±26	636±32
	in mg./100 g.	364	355	472	381
Kidney	in mg.	715±8·9	1,501±259	658±58	1,028±36
	in mg./100 g.	500	698	639	615
Liver	in mg.	5,661±392	11,756±409	5,114±771	9,226±224
	in mg./100 g.	3,959	5,468	4,965	5,524
Adrenals	in mg.	38±0·39	66±6·5	12±0·48	22±2·6
	in mg./100 g.	26·4	30·8	12·2	13·2
Thymus	in mg.	136±27	171±54	29±3·7	34±4·6
	in mg./100 g.	95	79	28	20
Spleen	in mg.	780±50	1,286±655	373±54	1,146±409
	in mg./100 g.	545	598	362	686
Preputials	in mg.	47±2·8	101±48	55±10	174±13
	in mg./100 g.	33	70	53	104

TABLE IV.—*Summary of Some Clinical and Histological Observations in the Second Experiment*

Group:	I Normal Controls	II S.T.H. (Li)	III Cortisone	IV S.T.H. (Li) +Cortisone
Myocarditis	0	++	0	0
Nephritis+nephrosclerosis	0	++	0	0
Pancreatic periarteritis	0	+	0	0
Water intake in ml.	43±2	191±21	73±4·5	62±3·9
Blood pressure in mm. Hg	136±3	155±5	154±7	175±19
Arthritis test	++	+++	0	++

It will be seen that under these experimental conditions S.T.H. (Li) produced marked cardiac and renal enlargement as well as diuresis, all of which were inhibited by simultaneous cortisone treatment. Significantly, at the dose level at which it was employed here, cortisone caused marked adrenal atrophy despite S.T.H. treatment; it is tempting to ascribe the inhibition of the cardiovascular and renal effects to this cortical involution. Thus there is no reason to assume any important qualitative difference in the actions of the two S.T.H. preparations which we employed.

It will be noted that in this second experiment we also examined the *preputial glands*. These were only moderately influenced by cortisone or S.T.H. alone, but underwent a most pronounced enlargement in the rats treated with both these hormones simultaneously. The observation recalls some of our earlier experiments which showed that the atrophy of the preputial glands produced by hypophysectomy can be prevented by an impure anterior pituitary extract. The latter even causes preputial-gland enlargement both in intact and in hypophysectomized rats, this effect being considerably augmented by testosterone, androsterone, progesterone, and Δ^5-pregnenolone, but not by D.C.A. At that time pure gluco-corticoids (such as cortisone) were not yet available to us. From these observations we concluded "that the preputial gland stimulating effect (just as the mammogenic action) of steroids is at least partly dependent upon the simultaneous action of hypophysial hormones" (Selye and Clarke, 1943).

The present observations suggest that S.T.H. is the factor which was responsible for the stimulating effect of our impure anterior pituitary extract on the preputial gland. Experiments now under way in this Institute are designed to examine the specificity of this effect and its possible suitability for the bio-assay of S.T.H. Preliminary investigations have shown that, under suitable experimental conditions, S.T.H. causes marked preputial-gland enlargement within 48 hours. Perhaps the sensitivity of this test might be further augmented by topical application of S.T.H. We mention these preliminary findings only because of the urgent need for a clinically applicable sensitive bio-assay method for the estimation of S.T.H. in biological fluids. Perhaps they will stimulate others to explore such possibilities.

Discussion

The principal outcome of these experiments was to show that the mineralo-corticoid-like actions of L.A.P. can be reproduced by electrophoretically pure S.T.H. They also demonstrate that under suitable experimental conditions the concurrent administration of cortisone inhibits these effects of S.T.H., perhaps because it depresses A.C.T.H. secretion by the animal's own pituitary.

It had long been known that certain impure pituitary extracts contain a principle, "the L.A.P.-factor" or the "X-factor," which exerts mineralo-corticoid actions, presumably because it induces the adrenal cortex to secrete D.C.A.-like steroids. It was obvious that this factor is not the commonly known corticotrophic hormone A.C.T.H., because the latter produces gluco-corticoid actions by inducing the adrenal to secrete predominantly cortisone-like (or "compound F"-like) substances. The experiments reported here suggest that this X-factor is identical with S.T.H. In a certain sense, therefore, one might consider S.T.H. to be "mineralo-corticotrophic," just as A.C.T.H. is "gluco-corticotrophic." Yet there seems to be an essential difference between the mechanism of action of S.T.H. and A.C.T.H., in that the latter maintains adrenal weight even in the hypophysectomized animals, while S.T.H. fails to do so (Simpson *et al.*, 1949).

It will be recalled, however, that, on the basis of indirect evidence, we predicted that the "X-factor" in L.A.P. could exert its mineralo-corticotrophic actions only in the simultaneous presence of A.C.T.H. (Selye, 1950b). Thus, A.C.T.H. would be required not only for the secretion of gluco-corticoids but also for the maintenance of the adrenal cortex in a condition of responsiveness to S.T.H. In this event, when A.C.T.H. is eliminated, either by hypophysectomy or by the administration of adequate amounts of cortisone, then S.T.H. of course could not exert its mineralo-corticotrophic effects. The above interpretation is all the more probable since some of our unpublished data showed that A.C.T.H. injections increase the ability of S.T.H. to produce cardiovascular and renal damage with severe polyuria. (Incidentally, this is one of the few respects in which A.C.T.H. and cortisone exhibit diametrically opposite effects.)

Another fundamental difference between the actions of the two pituitary principles is that A.C.T.H. does not appear to produce any direct actions; hence it is ineffective in the absence of the adrenals. On the other hand, S.T.H. stimulates somatic growth even after adrenalectomy (Emery and Gottsch, 1941). It may be added that in the experiments reported here we often noted the development of fibroma-like connective-tissue proliferations at the site of S.T.H. injections. Preliminary observations (unpublished) showed, furthermore, that the injection of S.T.H. into the joint region (using our technique for the production of topical irritation arthritis) causes very extensive granuloma formation in the peri-

articular structures. Here we are obviously also dealing with a direct effect of S.T.H. Perhaps the development of experimental replicas of the so-called "collagen diseases" under the influence of S.T.H. overdosage is dependent upon a dual mechanism—namely, the production of mineralo-corticoids by the adrenals and the direct stimulation of connective-tissue proliferation by the S.T.H. itself.

It is probably because of this dual action that S.T.H. overdosage does not merely copy the manifestations of D.C.A. intoxication. Large doses of S.T.H. reproduce the effects of excessive D.C.A. administration in the cardiovascular system and the kidney, but the syndrome produced by S.T.H. intoxication is invariably also accompanied by the specific actions of the latter hormone upon somatic growth in general, the spleen, the liver, etc. These latter changes cannot be duplicated by D.C.A. Presumably, S.T.H. stimulates the proliferation of connective tissue and its ability to respond with granuloma formation upon local injury, both by the production of mineralo-corticoids and by some of its direct peripheral effects. Through this peripheral action S.T.H. presumably sensitizes the connective tissues to the actions of the mineralo-corticoids discharged by the adrenal cortex under the influence of this same pituitary hormone.

We have seen that the cardiovascular and renal damage caused by S.T.H. intoxication is prevented by cortisone only if the latter hormone succeeds in producing a pronounced adrenocortical atrophy. This agrees with the view that the above-mentioned toxic actions of S.T.H. are mediated through the adrenal cortex. Conversely, under experimental conditions which prevent the production of adrenocortical atrophy by cortisone, the toxicity of S.T.H. is further aggravated by this steroid. This agrees with our previous finding that the nephrotoxic effects of mineralo-corticoids (e.g., D.C.A.) are likewise enhanced by cortisone.

In other respects the interaction is less predictable between exogenous (e.g., injected D.C.A. or desoxocortisone) and endogenous mineralo-corticoids (e.g., those produced under the influence of S.T.H.) on the one hand, and exogenous (e.g., injected cortisone) or endogenous gluco-corticoids (e.g., those produced under the influence of A.C.T.H.) on the other hand. The production of mesenteric periarteritis nodosa by mineralocorticoids is readily inhibited by gluco-corticoids, but the accompanying cardiac and pancreatic periarteritis nodosa may be prevented or aggravated by them, depending upon conditions (Selye, 1950b). L.A.P. (which contains both S.T.H. and A.C.T.H.) regularly causes marked renal damage, while cardiac lesions and pancreatic periarteritis nodosa are less common and mesenteric periarteritis nodosa is hardly ever observed. The resulting syndrome corresponds closely to that obtained by concurrent treatment with D.C.A. and cortisone.

In animals simultaneously injected with L.A.P. and cortisone the above-mentioned lesions are particularly severe, presumably because the A.C.T.H. contained in the L.A.P. prevents the compensatory adrenal atrophy normally elicited by cortisone; hence only the detrimental extra-adrenal synergism between the two preparations can manifest itself (Selye, 1951a). A similar aggravation of the L.A.P. effect is obtained by simultaneous treatment with pure A.C.T.H. (Selye, 1951b), probably for similar reasons. In both these cases the adrenal cortex is well developed and presumably maintains its responsiveness to S.T.H.

Electrophoretically pure S.T.H. is not yet abundantly available. However, it has been possible to show in the rat that the malignant nephrosclerosis and myocarditis normally produced by conjoint treatment with L.A.P. and cortisone can be completely prevented by adrenalectomy. As cortisone does not produce such renal and cardiac lesions either in intact or in adrenalectomized animals, it is probable that the active principle of L.A.P. (presumably S.T.H.) exerts its cardiotoxic and nephrotoxic effects through (or at least under the influence of) the adrenals.

It is particularly significant that adrenalectomized animals maintained on cortisone are highly resistant to normally lethal doses of L.A.P. In one such experiment two groups of rats were treated with cortisone and L.A.P. simultaneously; one group was adrenalectomized, the other not. The rats in possession of their adrenals died from nephrosclerosis and myocarditis when their adrenalectomized partners still survived in good condition. Here we are faced with a rather unusual situation in that adrenalectomy preserves life (Selye, 1951c, in press). This experiment will be repeated, using pure S.T.H. instead of L.A.P., in order to make certain that, in this respect also, the former is the active principle of the latter. It is already obvious, however, that some factor present in our anterior pituitary preparation exerts its fatal effects only in the presence of the adrenal cortex, presumably through the liberation or activation of D.C.A.-like compounds.

One additional pertinent fact must be considered. In a hitherto unpublished experimental series, pure S.T.H. and D.C.A. were administered, either singly or in combination, to rats sensitized to mineralo-corticoid actions (by unilateral nephrectomy and a high NaCl intake). Here concurrent administration of S.T.H. and D.C.A. produced fatal nephrosclerosis and myocarditis much more rapidly than either of the hormones given alone. Thus there is an obvious synergism between S.T.H. and the mineralo-corticoid substance D.C.A.

Conclusions

Under suitable experimental conditions, electrophoretically pure somatotrophic hormone (S.T.H.) produces cardiovascular and renal changes quite similar to those elicited by toxic doses of mineralo-corticoids.

Cortisone in doses capable of producing adrenocortical atrophy, or surgical removal of the adrenal glands, prevents the above-mentioned lesions, which are normally elicited by pure S.T.H. or by S.T.H.-containing anterior pituitary preparations. On the other hand, both A.C.T.H. and D.C.A. aggravate these S.T.H. actions.

As regards the mechanism through which S.T.H. could exert its toxic effects upon the cardiovascular system and the kidney, the following possibilities come to mind:

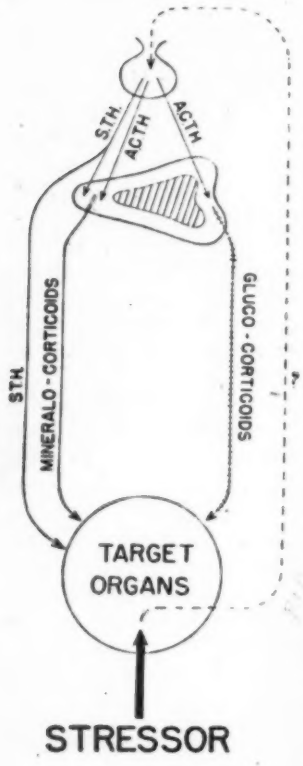
1. A.C.T.H. is a gluco-corticotrophic hormone—that is, one which stimulates the adrenal to produce gluco-corticoids—and S.T.H. possesses mineralo-corticotrophic effects. However, while A.C.T.H. can maintain the integrity of the adrenal cortex—for example, even after hypophysectomy—S.T.H. fails to do so. Hence the latter cannot elicit its potential mineralo-corticotrophic actions after the adrenal cortex has become atrophic owing either to cortisone overdosage or to hypophysectomy.

2. The secretion of mineralo-corticoids by the adrenal cortex is independent of hypophysial regulation. However, owing to a peripheral synergism, the mineralo-corticoids (such as D.C.A.) sensitize, while the gluco-corticoids—for

example, cortisone—desensitize, the tissues to the above-mentioned toxic effects of S.T.H.

3. S.T.H. exerts its effects both through the adrenal cortex and in the periphery. It augments mineralo-corticoid secretion and at the same time sensitizes the tissues to the effects of mineralo-corticoids. Conversely, gluco-corticoids diminish the production of either type of corticoid and concurrently desensitize the tissues to the mineralo-corticoid (D.C.A., S.T.H.) type of effect.

Further experiments are now in progress to verify the correctness of these three possibilities, but at the present time the third hypothesis seems to be most readily compatible with all the known facts. It is illustrated by the accompanying diagram.



Schematic Diagram Illustrating the Principal Interrelations Between the Hypophysis, the Adrenal Cortex, and the Peripheral Target Organs During the General-adaptation Syndrome. — The *stressor* (trauma, infection, burns, etc.), acting upon the cells, evokes a stimulus which induces the anterior pituitary to produce A.C.T.H.; in certain circumstances it may also cause a discharge of S.T.H. The nature of this first mediator between the directly injured organ and the anterior pituitary is not yet known (humoral, nervous ?). Hence here it is indicated merely by an interrupted line, labelled with a question mark. *A.C.T.H.* induces the adrenal cortex to produce predominantly *gluco-corticoid* compounds, whose effect upon the response of the various target organs is generally inhibitory—for example, catabolism, diminution of granuloma formation and of allergic responses. Conversely, *S.T.H.* enhances a variety of defensive reactions in the target organs—for example, anabolism, augmentation of granuloma formation and of allergic responses—primarily by stimulating the connective tissue. Part of this action is undoubtedly not mediated through the adrenal cortex, but this direct effect sensitizes the connective-tissue elements to the—essentially similar—actions of the *mineralo-corticoids*. It is probable that S.T.H. also acts by increasing the production of mineralo-corticoids. However, in itself it cannot maintain the cortical cells in a responsive condition, hence its "corticotrophic" effect is dependent upon the simultaneous availability of A.C.T.H. In the final analysis the physiological and pathological responses of the target organs to stressor agents largely depend upon the balance between the mineralo-corticoids and S.T.H. on the one hand, and A.C.T.H. and the gluco-corticoids on the other.

Summary

Experiments on female piebald rats revealed that electrophoretically pure somatotrophic hormone (S.T.H.) produces nephrosclerosis with variable degrees of nephritis, marked polyuria, myocarditis, pancreatic periarteritis nodosa, and hypertension. The experimental animals were sensitized to mineralo-corticoid actions by unilateral nephrectomy and an excess NaCl intake, but this sensitization in itself did not produce such changes.

The type of the toxic manifestations, as well as the sensitization of the animals to these S.T.H. effects by unilateral nephrectomy and NaCl, parallel our previous findings in animals receiving excesses of desoxycorticosterone acetate (D.C.A.) or lyophilized anterior pituitary (L.A.P.) material.

It is assumed that S.T.H. is the active principle responsible for the toxic actions of L.A.P. upon the kidney and the cardiovascular system. The lesions caused by S.T.H. are considered to be, in all likelihood, secondary to a sensitization of the tissues to D.C.A.-like mineralo-corticoids. In addition, S.T.H. may also increase the production of mineralo-corticoids by the adrenals.

The cardiovascular and renal damage normally caused by S.T.H. overdosage is prevented if cortisone is simultaneously administered in doses adequate to produce adrenocortical atrophy.

S.T.H. increases the sensitivity of the rat to the production of experimental arthritis. Simultaneous treatment with cortisone exerts a contrary effect. However, larger doses of cortisone are required to inhibit an experimental arthritis in the S.T.H.-treated than in the otherwise untreated animal. Apparently the anti-arthritic effect of cortisone is inversely proportional to the amount of S.T.H. present in the organism

In the production of the so-called "diseases of adaptation" S.T.H. appears to play a part equally as important as that of A.C.T.H. The former is responsible for the activity of mineralo-corticoids, which stimulate defensive granuloma formation, while the latter regulates the secretion of gluco-corticoids, which inhibit such defence reactions.

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When they met last September, the Expert Committee on Tuberculosis of the World Health Organization drew attention to the value of routine chest examinations in general hospitals as a way of detecting unsuspected cases of tuberculosis. They quoted experience in the United States, where 247 general hospitals are now taking *x*-ray pictures of all out-patients, admissions, and hospital staff. In one hospital in New York State, for example, where a total of 7,187 patients (74%) were radiographed, 290 (4%) showed signs of tuberculosis. At the Chicago University dispensaries 15,000 people have been examined in this way since the start of the scheme in 1942, and again over 4% of them showed tuberculous lesions. From this and other studies in Chicago—for example, a survey of 25,000 negroes—it has been suggested that there are in the U.S. something like 600,000 patients undergoing medical treatment for other complaints while they have active undiagnosed tuberculosis. The Committee recommends that general hospitals should take up this challenge.

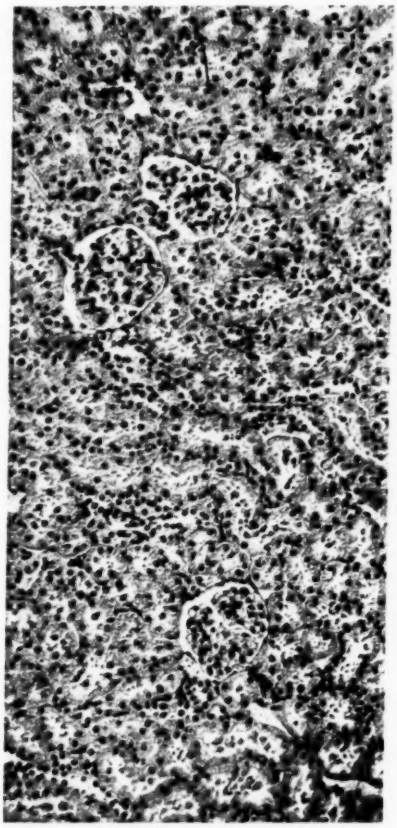

FIG. 1.—Kidney of control rat (group I). Note normal appearance of glomeruli and tubules.

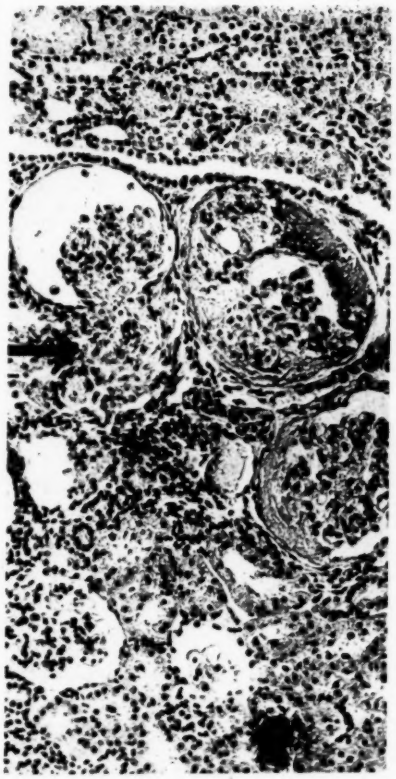

FIG. 2.—Kidney of S.T.H. (Li)-treated rat (group II). Intense hyalinization of some glomeruli; distension of Bowman's capsules and some tubules. Arrow indicates markedly hyalinized and almost occluded afferent glomerular arteriole.

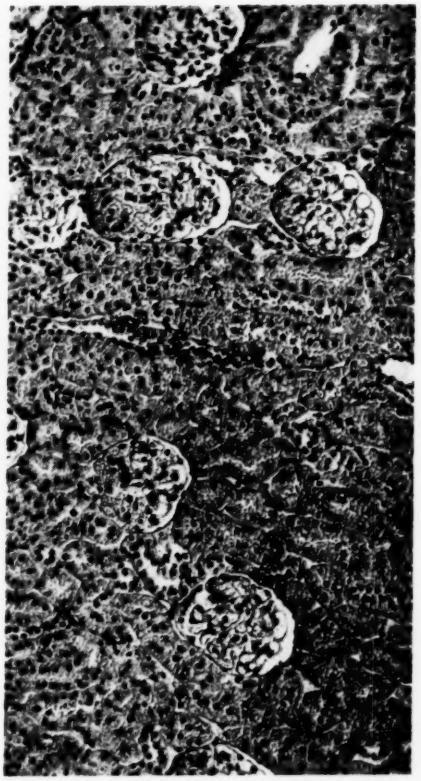

FIG. 3.—Kidney of cortisone-treated rat (group III). Extraordinary hyperaemia of glomeruli, with dilatation of glomerular capillaries. Arterial system and tubules not affected by cortisone.

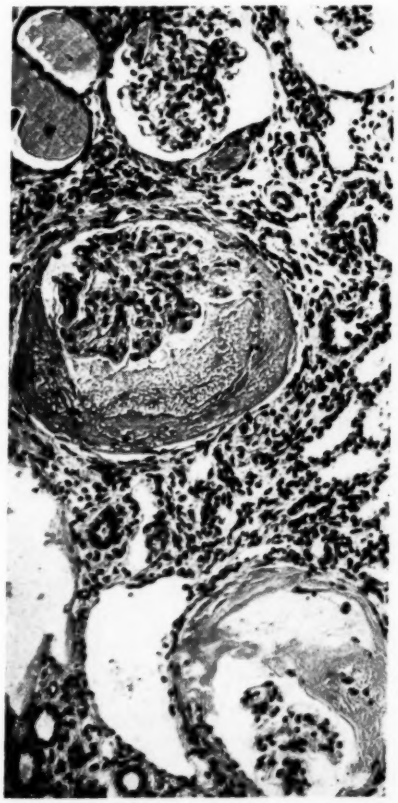

FIG. 4.—Kidney of rat treated with S.T.H. (Li) and cortisone (group IV). Glomerular and tubular changes even more pronounced here than in animal illustrated in Fig. 2.

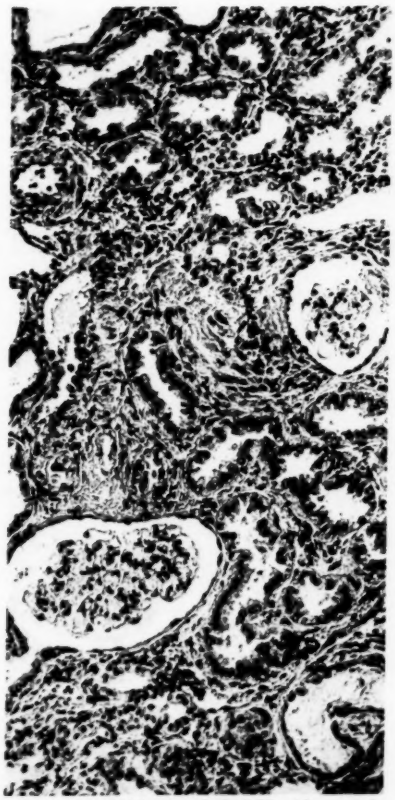

FIG. 5.—Kidney of S.T.H. (Armour)-treated rat (group V). Changes are essentially similar to those produced with S.T.H. (Li), though their frequency in this group was considerably less.

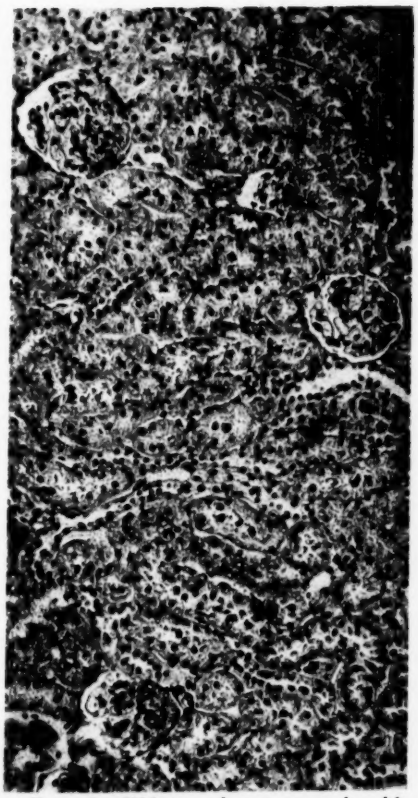

FIG. 6.—Kidney of rat treated with S.T.H. (Armour) and cortisone (group VI). Nephrosclerotic and nephritic changes completely suppressed, though glomerular hyperaemia characteristic of cortisone is detectable.

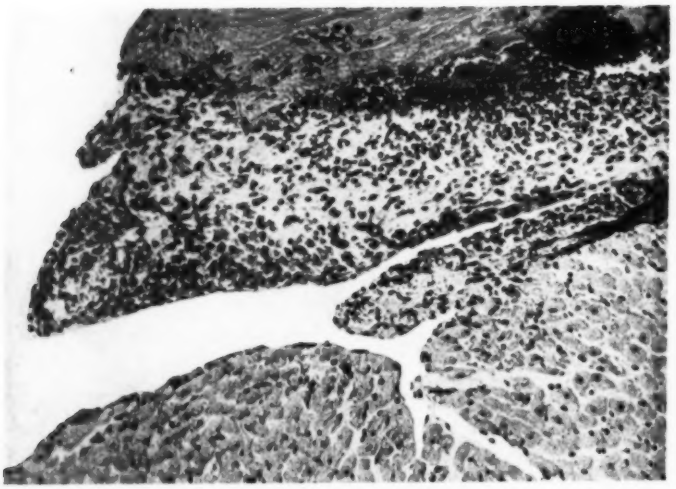

FIG. 7.—Insertion of mitral valve in rat treated with S.T.H. (Li) and cortisone (group IV). Infiltration of valve by inflammatory cells and deposition of fibrinous material at site of an endothelial defect.

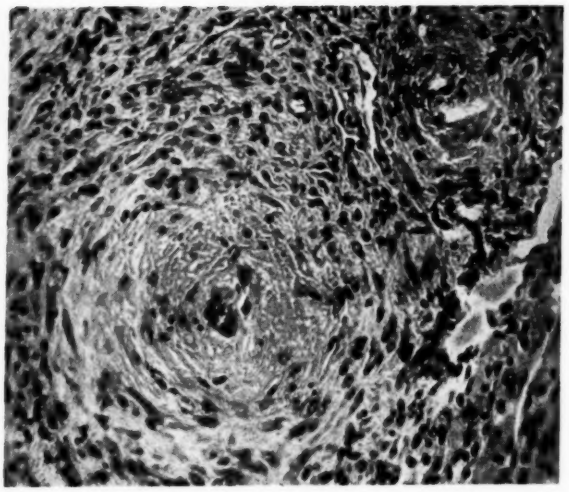

FIG. 8.—Arteriole from pancreas of rat treated with S.T.H. (Li) (group II). Hyalin necrosis of the vessel wall with proliferation of typical granuloma tissue.

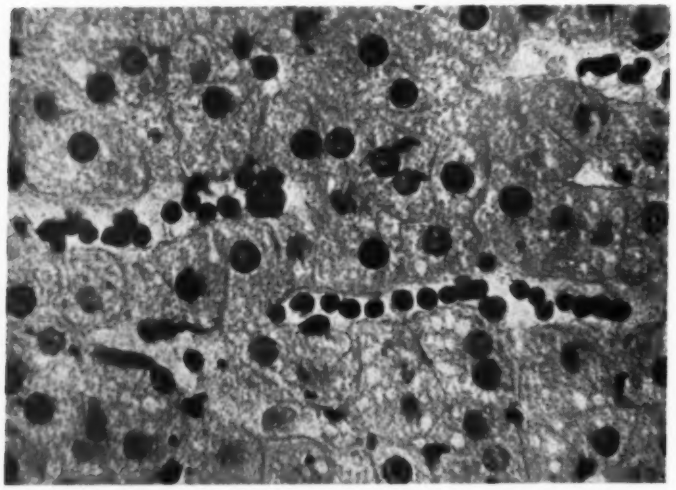

FIG. 9.—Adrenal of rat treated with S.T.H. (Li) (group II). Extraordinary predominance of small lymphoid elements within the cortical sinusoids.

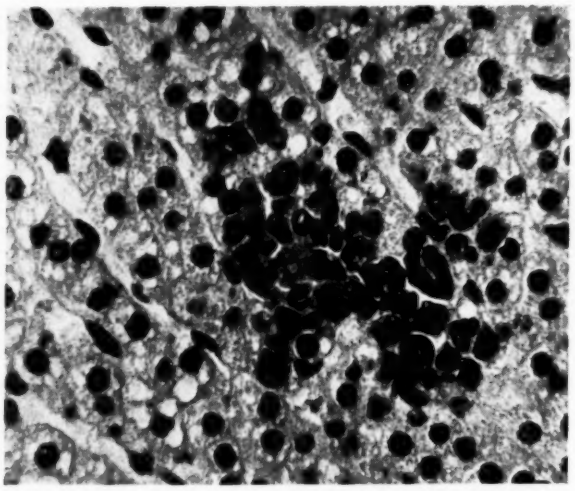

FIG. 10.—Another region from the adrenal shown in Fig. 9. Note appearance of lymphoid and myeloid elements between the cortical cells.

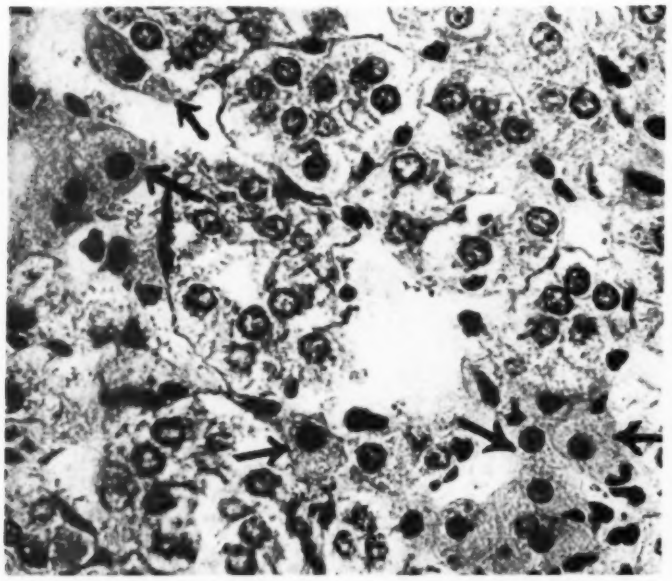

FIG. 11.—Adrenal medulla from a rat treated with S.T.H. (Li) (group II). Hypertrophy of several typical cortical cells (indicated by arrows) interspaced between the medullary elements.

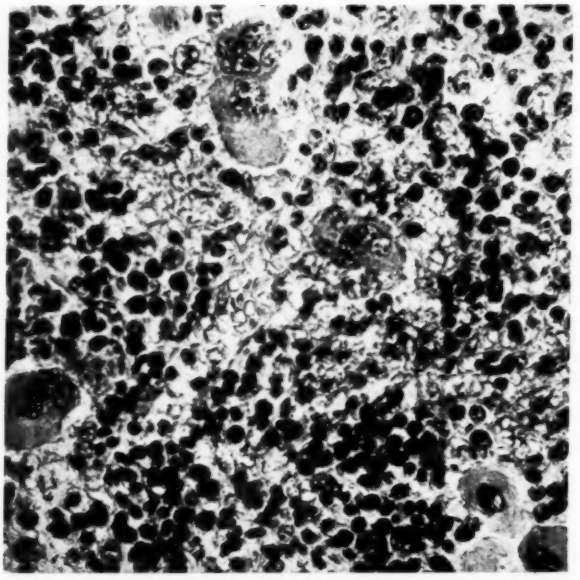

FIG. 12.—Many large megakaryocytes in spleen of rat treated with S.T.H. (Li) (group II). There were also many eosinophilic granulocytes in the spleen, but they are not readily distinguishable here.

A METHOD FOR DETECTING CORTISONE IN BODY FLUIDS

BY

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The pioneer work of Venning *et al.* (1946) in studying the urinary excretion of cortisone-like steroids in the urine in various disease states has been followed by relatively little research confirming and extending their observations. This has been largely due to the laborious and time-consuming methods of assay which they had to employ. With the increasing recognition of the widespread influence of cortisone in so many disease processes, and the growing interest in the behaviour of the adrenal gland in these diseases, the need for simpler methods for detecting and assaying such substances in body fluids has become great.

There are several chemical methods for estimating the urinary products of adrenal metabolism, based on their chemical properties, particularly their reducing power and their ability to liberate formaldehyde. In the course of investigations using these chemical methods we formed the impression that the variations in chemically determined steroid in the urine do not parallel the changes in cortisone content (Cope, 1951). The latter, indeed, represents only a small fraction of the reducing steroid found to be present by chemical means.

A method has therefore been developed for detecting the compounds cortisone and 17-hydroxycorticosterone in body fluids which is based on the specific ability of these compounds to reduce the number of circulating eosinophil cells in the blood. Suitably prepared extracts of urine or other body fluids are injected into adrenalectomized mice and the subsequent percentage fall in blood eosinophil cells is measured. A roughly proportional relation can be shown between the extent of this fall and the amount of cortisone injected.

Preparation of Urine Extracts

A 24- or 48-hour collection of urine without preservative, preferably checked for completeness by determination of its creatinine content, is acidified to the extreme range of thymol blue (approximately *p*H 1) with concentrated sulphuric acid. It is stood at room temperature overnight and then extracted by shaking in separating funnels with four successive quantities of chloroform, each being equal to 15% of the urine being extracted. The resultant chloroform emulsions are centrifuged clear of aqueous phase in a large centrifuge. The clear chloroform phase is evaporated under reduced pressure to a volume of about 30 ml., the temperature of the water bath being kept below 50° C. throughout the distillation. The concentrated chloroform extract is transferred quantitatively to a small separating funnel and is washed three times with N/10 soda (6 ml.) and then three times with water (6 ml.), each washing being back-extracted with chloroform, which is added to the extract. The washed chloroform solution is then evaporated to dryness under reduced pressure at a temperature below 50° C.

Solvent for Injection.—The solvent found most suitable is propylene glycol: 0.2 ml. of this is added to the dried extract. The tube is gently warmed to about 45° C. and is rotated slowly until the extract is fully dissolved. Normal saline, 0.8 ml., is then added, and the tube is shaken to give a homogeneous mixture. Some precipitation may occur on dilution, but this seems to be unimportant.

Adrenalectomized Mice.—Mice have been adrenalectomized by single-skin and bilateral-muscle incision. The best anaesthetic has been found to be 1.5 to 2 mg. of pentobarbitone sodium subcutaneously, supplemented by small quantities of open ether. Only mice from which both adrenals have been successfully removed without rupture are used for the tests. They are maintained on saline (1%) and full diet for at least four days before use. The same animals may be used for several tests on different days.

The Eosinophil Test

Blood is drawn from the tail vein to the 0.5 mark on a white-cell pipette. In a well-warmed room no difficulty is found in obtaining enough blood by a razor cut across one of the four tail veins. The blood is diluted to the top mark with Randolph's diluting fluid, and eosinophil cells are counted in duplicate in the Fuchs–Rosenthal chamber. Randolph's (1944) diluting fluid consists of 0.1% phloxine and 0.1% methylene blue, each dissolved separately in 50% propylene glycol. The two solutions are mixed in the proportion of two parts of phloxine solution to one part of methylene blue solution immediately before use. The eosinophils are very stable and are easily recognized in this diluent, but they require about 15 minutes to stain and to settle in the counting chamber.

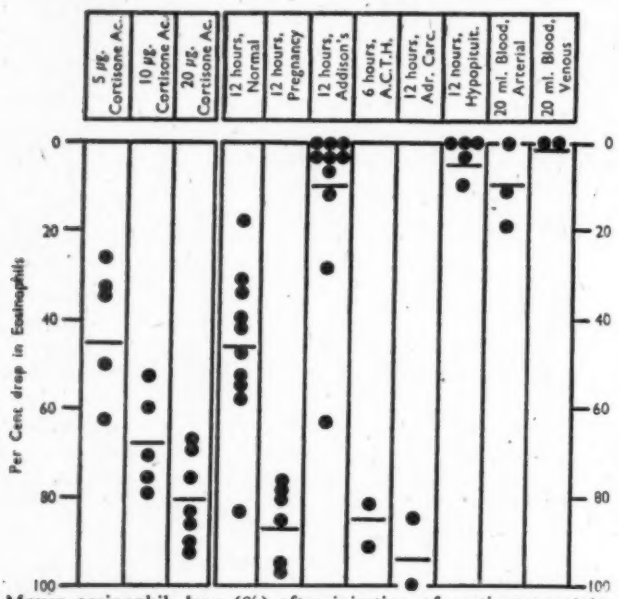
The equivalent of 12 hours' urine extract in 20% propylene glycol is then injected subcutaneously and the animals are returned to their cages. The volume of the injection should not exceed 0.5 ml. Further eosinophil counts are done at four and again at six hours after injection. The original tail cut will usually provide blood for these two further samples.

Interpretation.—The significant response is the maximum drop in eosinophil cells expressed as a percentage of the initial value. This drop may be greatest at either four or six hours. Spontaneous rises above starting value may occur after injection of inert extracts, when they are interpreted as zero fall. Only a very small activity of the extract seems to be enough to prevent such spontaneous rises. It appears that the tendency of cortisone-like substances to drop the eosinophils is a much more potent stimulus than the tendency of minor trauma or other factors to produce a rise in eosinophils in the adrenalectomized mouse. Propylene glycol alone does not affect the eosinophil level, though it has been found an unsuitable solvent for assay of these steroids by the glycogen storage method. Speirs and Meyer (1949) have studied the behaviour of mouse eosinophils under laboratory conditions.

Results

Preliminary work with this method has been more concerned with general variations than with careful assay of individual urine specimens. An accurate dose-response curve has therefore not been attempted on large groups of animals. A small series of trials has, however, been made to determine the sensitivity of the test to cortisone-like substances. Five-microgram doses of cortisone acetate gave a mean depression of the eosinophil count of 45%, 10-μg. doses a mean drop of 68%, and 20-μg. doses a mean drop of 80.5%. Even with these small animal groups the tendency to a response proportional to the logarithm of the dose is apparent. Individual variations in response are indicated graphically in the accompanying Chart.

The response to extracts of normal urine is fairly wide, but the drop in eosinophil count, after the equivalent of 12 hours' urine from "normal" hospital patients, is usually between 20 and 60% under the conditions we have used, the mean for a small group being 46%. This is equivalent to about 10 μg. of cortisone a day. Such a figure is considerably lower than has been found by other methods (Venning *et al.*, 1946), and a considerably higher amount has actually been isolated from



Mouse eosinophil drop (%) after injection of cortisone acetate, urine extracts, and blood extracts.

normal urine (Schneider, 1950). Our own low results may be due to the method of preparation of the extract and to other factors. At present, therefore, we do not attach significance to the absolute figure, but stress rather the value of the method for comparative purposes and for following changes under various conditions.

In contrast to the normal urines, ten extracts of urine from four cases of Addison's disease showed much lower average activity. Seven of these had no activity, and only two had activity as great as the normal. These two active extracts were both derived from a patient whose Addison's disease was clinically mild and who had active pulmonary tuberculosis. The mean drop for all ten extracts in this group was 10%. Five extracts from three cases of panhypopituitarism gave no significant drop in the eosinophil count. A pooled extract derived from five patients all eight months pregnant gave eosinophil depressions in six mice equivalent to about 25 μg. of cortisone a day, a figure more than twice that found in normal urine. Another pooled extract of urine excreted during A.C.T.H. administration was tested at several dose levels and gave a response equivalent to 120 μg. a day. Similarly, an extract from the urine of a woman with advanced adrenal cortical carcinoma with metastases, and associated with many features of Cushing's syndrome, was tried in 12-, 6-, and 3-hour doses, and indicated an excretion of about 40 μg. a day, or about four times the normal average.

Several specimens of blood have been tested, a different method of extraction being necessary. Two 20-ml. samples of venous blood showed no activity, but in two of three 20-ml. samples of arterial blood slight activity was suggested. Much further trial is required before this difference can be regarded as significant.

Comment and Conclusions

The method proposed has been found a useful and practical one for detecting cortisone-like activity in urine extracts. Its applicability to blood is uncertain. Preliminary results with the method show activity in normal urine extracts and a raised excretion in late pregnancy, during A.C.T.H. administration, and in a case of adrenal cortical carcinoma. The cortisone-like activity was absent from the urine of most cases of Addison's disease and from three cases of hypopituitarism.

Further work is needed before the method can become established as a reliable one for quantitative assay. When expressed in terms of cortisone acetate the activity found in normal urine and in late pregnancy is lower than was found by Venning *et al.*, using the glycogen storage method. The cause of this discrepancy is being investigated.

Since this work has been completed observations on similar lines have been reported by Rosemberg and Lewis (1950).

My thanks are due to the Medical Research Council for a generous gift of cortisone acetate, and to Miss Xenia Boysen for technical assistance in the preparation of extracts and in the eosinophil counts.

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ADDENDUM.—Further work at present in progress indicates that the nature of the solvent has a large effect on the rate of absorption of cortisone and, therefore, on the eosinophil depression resulting from a given dose. The responses shown in the first three columns of the chart were obtained with cortisone acetate in saline suspension. When, however, the injected cortisone acetate is dissolved in a volume of 20% propylene glycol equal to that used for our urine extracts a much smaller eosinophil drop occurs. The responses to our normal urine extracts, when compared with cortisone acetate injected under identical conditions, are then equivalent to daily cortisone outputs averaging 50 μg. The cortisone equivalent of other extracts is correspondingly increased, and these then become comparable to those found by Venning *et al.*

UNUSUAL AURAE IN TWO CASES OF EPILEPSY IN CHILDHOOD

BY

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The term "aura," in relation to seizures, was introduced into medicine in A.D. 100 by Pelops, the instructor of Galen, although the Corpus Hippocratica (see the book *De Morbo Sacro*) witnesses that premonitory subjective symptoms ushering in seizures were not unknown to earlier Greek physicians. The first attempt at systematic description of such seizure prodromata was that made by Aretaeus of Cappadocia early in the second century A.D. Since his account the varieties of epileptic aura that have been described are legion. In more recent times they have been the subject of detailed study and classical account by Hughlings Jackson (1931–2), Gowers (1901, 1907), Penfield and Gage (1933), Penfield and Erickson (1941), and Kinnier Wilson (1941).

This communication describes two cases of epilepsy in childhood which are notable for the unusual nature of the pre-ictal phenomena. Such phenomena are of interest because they probably represent the initial expression of the epileptic discharge, and as such are pertinent to the problems of cerebral localization of function.

Case 1

A girl aged 6 was referred to Dr. W. Ritchie Russell by Dr. O'Connell, complaining of frequent seizures since the age of 2½ years. The child was the product of a normal pregnancy and labour, and is the second in the family; the other child is perfectly normal. There was no family history of seizures on either side or of earlier infantile convulsions. There were no complaints other than the seizures.

Description of Typical Seizure

All the seizures have been of the same type, and have not varied in character over the past 3½ years. They usually occur early in the morning just after the child awakes. There is no preliminary cry, but after a few minutes' profuse salivation she suddenly vomits without any preliminary abdominal discomfort. Every seizure is ushered in by this unheralded vomiting, and it is not until after this that the real ictus begins: she is quite conscious during the vomiting phase, but has no memory of it after the seizure. The child has no warning of the onset of a seizure until this sudden unexpected vomiting, which has therefore come to constitute for her an epileptic aura.

After the vomiting her eyes turn upwards, and at this stage she loses consciousness, continuing to salivate profusely. Her mother describes the remainder of the seizure as consisting of slight twitching of the whole body, following upon a mildly opisthotonic phase. Urinary incontinence has occurred on a number of occasions, and sometimes the child has bitten her tongue. There is no post-ictal drowsiness.

These seizures have occurred about five or six times a year, and do not seem to be increasing in frequency. The child is right-handed. There are no abnormal physical signs in any system, the fundi are normal, and the visual fields are full. The child is very intelligent, with a good school record, though rather shy and at times excitable.

E.E.G. Studies (Fig. 1)

Electroencephalographic examination reveals a relatively stable occipital alpha rhythm at 10 cycles per second. It is rather better developed than one would expect at this age. It is of lower voltage on the left than on the right, and responds briskly to photic stimulation. Its average voltage is 60 to 70 microvolts in the occipital leads. Some lower voltage activity at 10 c./s. is also visible in the paracentral and frontal leads. During the resting record there are paroxysmal runs of slow activity in all leads, made up of mingled 4- and 6-c./s. waves, with an average voltage of 50 μV in the precentral leads and 80 μV in the frontal leads. This slow activity is bilaterally synchronous and symmetrical. Hyperventilation for one minute shows that the electrical activity of the cortex is markedly unstable, as there is considerable increase in the 4-c./s. waves on both sides of the brain. In places in the frontal leads there are short paroxysms of atypical wave-and-spike formations at 3 c./s. The post-hyperventilation record shows some persistence of this abnormality beyond the usual period. There are no focal disturbances.

Case 2

A boy aged 11 was referred to Dr. W. Ritchie Russell by Dr. D. Harris, having had about 50 seizures during the preceding year. There were no other complaints. All of the seizures occurred early in the morning, after he woke up screaming. He has had several further seizures since he first presented himself for examination, and all have the same chronology.

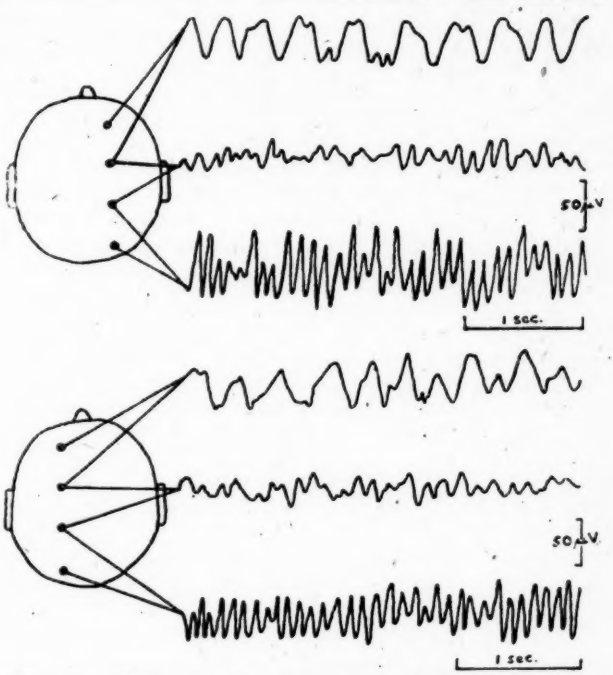

FIG. 1.—E.E.G. showing portion of a typical paroxysm in Case 1, immediately after hyperventilation for one minute. Calibration is indicated in the lower right-hand corner of each record. The origin of the discharges is indicated by the diagrams on the left.

Description of Typical Seizure

Each attack begins in the night or early morning with a loud scream, followed by a mild tonic phase, most pronounced in the arms and hands, together with turning of the head and eyes to the right. He then becomes unconscious, and shakes all his limbs, at the same time making unintelligible noises, with grimacing and smacking of the lips.

The interesting feature of this history is the child's precise description of the aura which precedes these attacks. Just before he screams he has an organized visual hallucinatory aura (see Fig. 2), in which he sees hundreds of objects

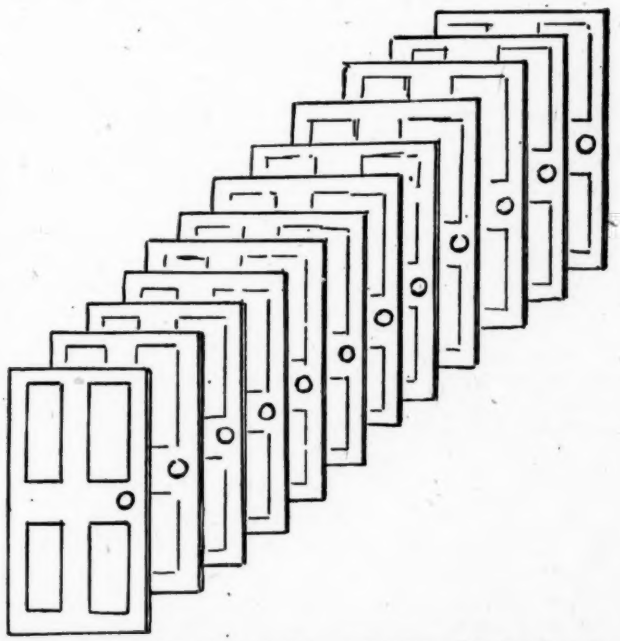

FIG. 2.—Drawing, elaborated from sketches made by Case 2, of an example of his reduplicative hallucinatory aura, representing the door of his bedroom as it appears immediately before a seizure.

ranged behind one another in a line receding from him into the distance and towards the right of his visual field. These objects always consist of some article of furniture or other object at which he is gazing at the time the fit begins, and he sees them only when the room is not absolutely dark. In complete darkness there is no visual aura whatever. The objects appear smaller than their normal size, as if they are far away, but each seems larger than the one in front of it. He describes the sensation as seeming as if the objects were seen in a number of mirrors many times reflected. There are no subjective olfactory or gustatory concomitants. His mother had a normal pregnancy and confinement at his birth, and he had no early infantile convulsions. There is no history of seizures on either side of the family. Physical examination discloses no abnormalities, the fundi are normal, and the visual fields are full. The child is extremely intelligent, bright, and co-operative, although somewhat wilful.

E.E.G. Studies (Fig. 3)

Electroencephalographic examination discloses an unstable alpha rhythm with a mean frequency of 9 to 10 c./s. and an average voltage of 25 to 30 μV, a little higher on the right than on the left. In the resting record there are short paroxysmal bursts of 4 c./s., 60- to 80-μV slow waves, synchronous on both sides of the brain, but of somewhat higher voltage on the right.

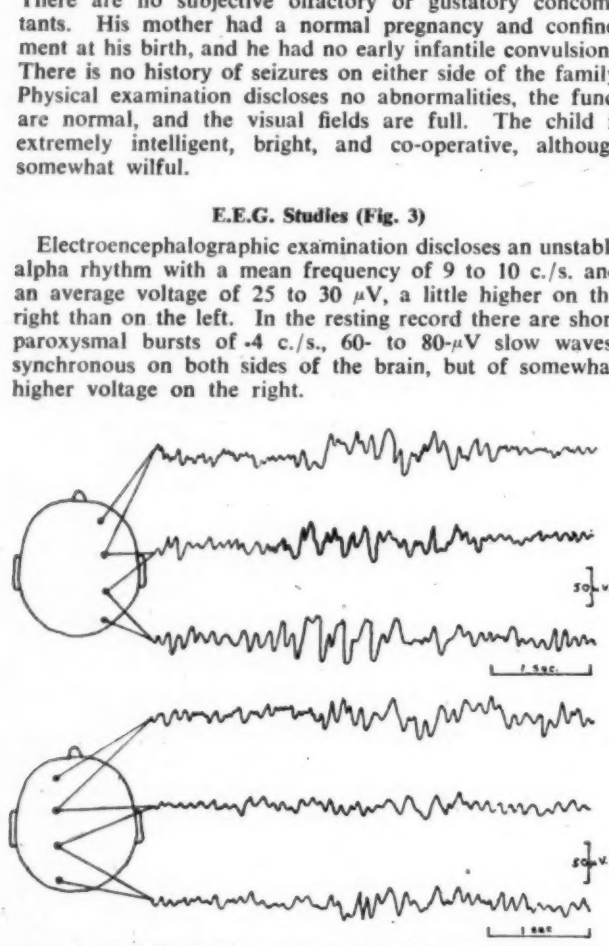

FIG. 3.—E.E.G. showing a typical dysrhythmic paroxysm in Case 2, immediately after hyperventilation for one minute. Calibration is indicated in the lower right-hand corner of each record. The origin of the discharges is indicated by the diagrams on the left.

Hyperventilation for one minute reveals marked electrical instability, with the rapid appearance of 80- to 100-μV 4-c./s. activity on both sides of the brain, including the temporal regions. During this period the patient usually becomes pale, and looks and feels as if he were going to have a seizure, but no such seizure is clinically apparent, although the typical aura is generally present. During the post-hyperventilation period paroxysmal bursts of 4-c./s. activity persist for several minutes.

Discussion

Case 1

The occurrence of unheralded vomiting as an introductory feature of an epileptic seizure is extremely rare, although various forms of abdominal disturbance (Vining, 1922; Watts and Frazier, 1935; Moore, 1944, 1945; Marchand and de Ajuriaguerra, 1948) are common, especially in children, in whom they may occur in up to 14% of cases (Patrick and Levy, 1924).

Sir William Gowers, in his Hughlings Jackson Lecture in 1907, mentions a case of a female child whose rightsided Jacksonian seizures were marked by vomiting in the initial phases of the seizure, but this did not occur until after the patient had lost consciousness. In earlier reports (Gowers, 1901) he had described three adult cases whose epileptic aura seems similar to that of the present case. One was a case with a vertiginous aura, in which nausea and vomiting preceded each major seizure. Another was a case in which minor seizures were preceded by extreme nausea as an aura, so that the patient took out his handkerchief on each occasion, expecting to vomit. The third case was one in which an aura of nausea was followed by vomiting before the fit began: later this aura was replaced by pre-ictal sialorrhoea and spitting, a fact which may be related to the marked salivation reported in the present case. These cases resemble earlier descriptions by Féré (1891, 1894) and Lemoine (1898). More recently Gram (1948) has reported the case of a child with episodes of vomiting accompanied by dysrhythmic episodes in the E.E.G.

In recent years Wilder Penfield (1949) and Wilder Penfield and Erickson (1941) have demonstrated that electrical exploration of the insula will often produce on the operating table a characteristic epigastric aura in patients who experience such sensations as an essential part of their seizures. It has also been suggested that such stimulation (Davey, 1949) may produce movements of the gut, intussusception, and occasionally vomiting. But, as Penfield has pointed out, effortless vomiting may occur after electrical stimulation of a wide variety of cortical areas.

Of interest to the present discussion, however, is a case noted by Penfield and Erickson (1941), in which a boy experienced a swimming sensation in the head, followed by a strong desire to vomit, as an introductory phase of his seizures. This sequence of events was found to be reproducible on the operating table by electrical stimulation of an area of softening in the left temporal lobe.

In this first case there was no evidence, either clinical or electroencephalographic, of focal disturbances related to the insula or temporal lobe; although in view of current physiological knowledge, principally that deriving from the studies of Penfield and his colleagues (Penfield and Gage, 1933; Penfield and Erickson, 1941), one might have expected to find an epileptogenic focus in the region of one or other fronto-temporal regions.

Case 2

The occurrence of organized visual hallucinations as an introductory epileptic phenomenon has also been well known since the time of Hughlings Jackson, and has been commented on by numerous writers. But the detailed description of the aura given by this young boy, and his sketches of some examples (Fig. 2), illustrate pre-ictal hallucinations of a type which has not often been recorded.

The only example of what might be called reduplicative imagery which I have been able to discover in the literature is a case mentioned by Kinnier Wilson (1941) in which 12 men arranged in a line were seen as a hallucination immediately preceding a grand-mal convulsion. Micropsia has been reported often enough (see Marchand and de Ajuriaguerra, 1948); and Gowers (1901) described several cases in which a visual aura consisted of an organized panorama seen in the far

distance. But there seems to be no case in the literature in which receding reduplicated images have been seen.

Another unusual feature is that the images are multiplications of objects actually seen—in the absence of illumination there are no hallucinatory phenomena. As these seizures were also characterized by turning of the head and eyes to the right and smacking of the lips, a left temporo-frontal focus was sought. It is generally considered that the occurrence of organized visual hallucinations indicates a disturbance in one or other temporal lobe, usually in the dominant hemisphere; and Penfield and Erickson (1941) and Marchand and de Ajuriaguerra (1948) classify seizures characterized thereby in the group of so-called "psychical seizures." In the present case, however, no clinical or electroencephalographic evidence of such a lesion could be found.

Conclusion

These two children have electroencephalographic records and clinical histories which suggest that they are suffering from a paroxysmal cerebral dysrhythmia of non-focal type. In each case the seizures are ushered in by unusual introductory phenomena, which, on current physiological grounds, might be expected to be related to disturbance in the anterior temporal lobe or island of Reil, but in which no evidence of such dysfunction can be found. It seems that these are cases of "idiopathic" epilepsy with unusual aurae, and as such have responded to treatment with phenobarbitone, with disappearance of seizures over the past year, during which time they have been under regular supervision.

My thanks are due to Dr. W. Ritchie Russell for permission to report these cases from his clinic, to Miss F. M. Taylor for carrying out the electroencephalographic examinations, and to Miss A. Arnott for working up the patient's drawings.

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Arguing that blood does not normally clot in the vessels because of the chemical nature of the endothelial lining of the vascular system, which is probably an acidic polysaccharide such as mucoitin, Drs. Lovelock and Porterfield have prepared (see *Nature*, January 6, p. 39) an artificial surface with a similar high negative (anionic) charge. They show that polystyrene tubes after a brief treatment with sulphuric acid are much better than untreated tubes and very much better than glass-ware in holding blood both fluid and free of clots.

SIXTH-NERVE PALSY AFTER LUMBAR PUNCTURE AND SPINAL ANALGESIA

BY

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Palsy of the sixth cranial nerve following spinal analgesia has been reported regularly since soon after the introduction of this method of pain relief, and it is perhaps a reflection on anaesthetists that most of the communications on this subject come from ophthalmologists. The incidence of the complication is difficult to determine. Mild degrees of abducens paralysis probably pass unnoticed or unheeded; and although the highest figure given, 1% of all spinal analgesics, by Terrien (1923) is considerable, it is possible that the figure should be considerably greater.

Paralysis of the various cranial nerves, except the first and tenth, has been reported, but there is general agreement that the sixth is most often involved. The lesion is discussed by many, including Mühsam (1906), Babcock (1913), Tovell (1933), Fairclough (1945), Steinberg and Bishop (1946), Rose and Pritzker (1947), Azambuja (1947), and Parke (1948).

Aetiology

The sequence of events is remarkably constant. The paralysis is not noticed until 3 to 21 days after the spinal analgesia, but it is preceded by a period during which the patient complains of severe headache and perhaps dizziness, nausea, stiff neck, photophobia, and diplopia. The delay in onset of the palsy has given rise to many theories about its causation, none of which is subject to proof. They may be summarized as follows:

1. *Mechanical.*—A rise in intracranial pressure causes a "coning" of the brain through the foramen magnum so that the sixth nerve (see Diagram), anchored between its entry into the cavernous sinus and its attachment to the pons, is stretched over the apex of the petrous portion of the temporal bone (Fairclough, 1945).

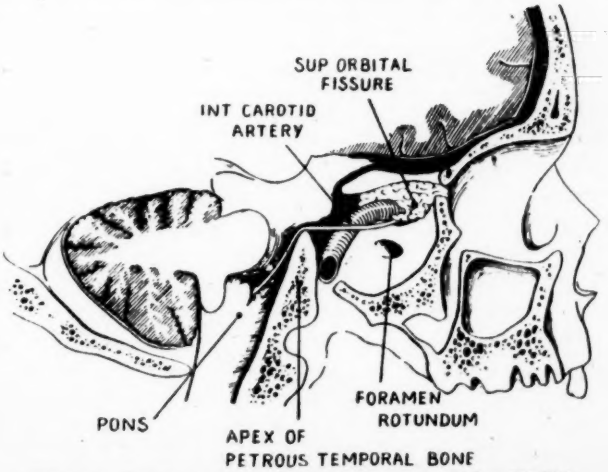

Diagram showing course of the sixth nerve. (After Wolff.)

2. *Toxic.*—This is specific degenerative change following the use of certain local analgesic drugs, and based on the known susceptibility of certain nerves to particular toxins—for example, the radial nerve to lead, and the posterior columns to ergot. If this theory were correct the lesion would be expected to be bilateral, whereas that is rarely the case. That procaine can cause nerve degeneration is known (Spielmeyer, 1908 ; Lundy, Essex, and Kernohan, 1933). Dinsdale (1947) has reported cauda equina lesions after the use of spinal analgesia, but the sixth nerve is never bathed in the high concentrations he mentions. Further, the complication has followed the use of a wide variety of drugs (Blatt, 1928) and even simple lumbar puncture for diagnostic purposes (Dattner and Thomas, 1941).

3. *Inflammatory.*—This implies a low-grade meningitis. Babcock (1913) attributed two cases of his to this. But the unilateral palsy and absence of an accompanying rise in temperature are good arguments against this view. The complication affects women slightly more often than men. The prognosis is favourable, and over 50% recover within a month of onset. On rare occasions the paralysis is permanent, and if after an interval of two years recovery has not taken place a corrective operation may be necessary. Generally the treatment is palliative. The troublesome symptom of diplopia is prevented by covering the affected eye with a shield, and the headache is relieved by suitable analgesics. Therapeutic lumbar puncture has been recommended with the object of lowering a supposedly raised intracranial pressure (Hayman and Wood, 1942), but the pressure of the cerebrospinal fluid may well be low and the procedure result in more harm than good.

Case Reports

Two cases have occurred recently in our hospital—one following simple lumbar puncture, the other after a spinal analgesic.

Case 1.—A woman aged 42 was to receive an extradural analgesic, but inadvertently the dura was pierced by a 16-gauge Tuohy needle, with the patient lying in the right lateral position. There was a rapid loss of about 5 ml. of cerebrospinal fluid through this large-bore needle. At this stage the technique was abandoned and a general anaesthetic given instead. The operation of cholecystectomy was uneventful. The next day the patient complained of nausea, pain in the back of the neck, and headache, aggravated on sitting up. Three days later double vision was remarked on. The next day there was a complete paralysis of the left lateral rectus muscle. It took three months for recovery to be complete.

Case 2.—A woman aged 49 was to undergo a total hysterectomy. An extradural analgesic was intended, but again an inadvertent spinal tap was made with a 16-gauge Tuohy needle. When the woman was lying on her left side, 8–10 ml. of cerebrospinal fluid was lost rapidly and the patient complained of severe frontal headache at that time. Light "nupercaine," 15 ml., was injected and the patient put lightly to sleep with a general anaesthetic. The next day complaint was made of headache, aggravated by sitting up, and slight nausea. Three days later double vision occurred, and on the seventh post-operative day partial paralysis of the right rectus muscle was evident. Recovery in this case was more rapid and was complete in six weeks.

These two cases have two points in common. A large-bore needle was used, causing a rapid loss of a comparatively large volume of cerebrospinal fluid, and external rectus paralysis developed in the eye opposite to the side on which she was lying. The brain, deprived of its water cushion through the sudden loss of cerebrospinal fluid, sags and a strain may be thrown on the sixth nerve, which is uppermost. The nerve is stretched, but the lesion is due primarily to reduced and not to raised intracranial pressure, as suggested by Fairclough.

When considering the pathogenesis of sixth-nerve palsy three facts should be borne in mind. The paralysis is preceded by headache. The causal relation of headache to prolonged seepage of cerebrospinal fluid through the hole made in the dura by lumbar puncture is now widely accepted (Franksson and Gordh, 1946). A patient suffering from a post-lumbar-puncture headache invariably assumes a horizontal position in bed, immobile and curled up on one side. These circumstances may account for stretching of the upper abducent nerve. In one-quarter of the reported cases the lesion is bilateral: the explanation may be that after some time the patient, by rolling on to the opposite side, exposes the other nerve to trauma.

We are grateful to Mr. E. Wolff, author of *The Anatomy of the Eye and Orbit*, for permission to modify and reproduce his original drawing.

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TORSION OF THE GREAT OMENTUM

BY

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Torsion of the great omentum is a well-recognized condition, but the number of recorded cases is still comparatively small. The torsion may be primary or secondary, complete or incomplete, and partial or total. Primary torsion where there is no recognizable cause is the less common. In secondary torsion, a hernia, neoplasm, cyst of omentum, tuberculosis, or evidence of past or present intraperitoneal inflammation is present.

Marchetti (reported by Aimès, 1919) is credited with having reported the first case of torsion of the great omentum in 1851. Oberst (1882), however, was the first to describe the condition. In each of these cases the condition was associated with an inguinal hernia. Eitel (1899) reported the first case of primary torsion. Corner and Pinches (1905) collected 54 cases from the literature. Morris (1932) collected a further 161 cases, and added three of his own, bringing the total number reported to 218. Etherington-Wilson (1945), in a critical review of the literature, reported 190 cases of torsion of omentum, 73 of which were considered to be primary or idiopathic. The number of cases reported by different authors varies. This is due to the fact that some authors have included cases in which torsion has been

confined to small tags or strips of omentum. Others have reported only cases in which torsion has involved the whole or greater part of the omentum. Taking Etherington-Wilson's figure as the basis, the number of cases recorded to date, including the three reported below, bring the total to 214, of which 80 are primary or idiopathic. Though the cause of torsion is still speculative, a number of theories have been advanced.

Payr (1902) ascribes the formation of intra-abdominal torsion to haemodynamic forces: a change in the relative position of the omentum from any cause, such as a sudden twist, or fluctuations in intra-abdominal pressure, may produce kinking. The stasis resulting in the tortuous veins favours the completion of torsion, and, finally, occlusion of the straight arteries occurs. Some writers have stated that the condition occurs more often in stout people: overloading or uneven fat distribution in the omentum increases the tendency to pedicle formation, and this in turn predisposes to torsion. The torsion usually presents itself in the right iliac fossa. This is explained by the fact that the right side of the omentum is the larger and more mobile. Thrombotic and embolic processes in the vessels of the omentum may be a factor in some cases, while violent bodily movements may predispose to torsion in others. Though any of the above conditions may produce torsion, probably several factors act together.

The following three cases illustrate some of the varied clinical features with which patients may present.

Case 1

A man aged 45 was admitted to Central Middlesex Hospital on February 16, 1946. On the day before admission he awoke with aching pain referred to the right hypochondrium. There was no nausea or vomiting. He continued at work all day, but had a restless night. The pain became much more severe a few hours before his admission.

On examination he appeared to be in great pain. His temperature, pulse, and respiration were normal. There were rigidity and tenderness of the whole of the abdomen on the right side, with an area of maximum tenderness just above and to the right of the umbilicus. There was no other abnormality in the abdomen or in any other system. The condition was diagnosed as atypical appendicitis.

Operation.—The abdomen was opened through a gridiron incision. The appendix was rather long and slightly thickened, but not inflamed. Further exploration of the abdomen revealed a semi-gangrenous piece of great omentum, about 3 by 2½ in. (7.6 by 6.3 cm.) in size, in the lower right hypochondrium, twisted anti-clockwise at its base. It was removed, together with the appendix. He had an uneventful convalescence, and left the hospital on March 4.

Case 2

A man aged 50 was admitted to Central Middlesex Hospital on November 16, 1948. He had suffered from right inguinal hernia for many years. Three days before his admission he felt a sudden pain in the right groin, followed by generalized abdominal pain, and the hernia became difficult to reduce. Since then he had had intermittent vomiting; the vomitus contained altered blood. The bowels were usually regular, but had not been opened on the day of admission.

On examination he was seen to be well nourished. His temperature was 102° F. (38.9° C.), pulse 120, and respirations 28. The abdomen was somewhat distended, and there was evidence of a moderate degree of free fluid in the peritoneal cavity. There was diffuse tenderness and guarding of the whole abdomen, more marked in the right iliac fossa; auscultation of the abdomen was normal. There was a large reducible indirect right inguinal hernia which recurred rapidly after reduction. It contained a firm tender mass which was thought to be omentum; other systems were normal. A straight *x*-ray film of the abdomen showed distended loops of small intestine containing fluid levels. There was no free gas under the diaphragm. A provisional diagnosis of strangulated internal hernia was made.

Operation.—The abdomen was opened through a right lower paramedian incision. The peritoneal cavity contained about a pint (570 ml.) of dark blood-stained fluid and the strangulated omentum presented itself. It was delivered into the wound and found to involve the whole of the great omentum, which was suspended by a narrow pedicle and had twisted four times on its long axis (Fig. 1). The omentum appeared very bulky and had a number of accessory projections; one of these projections along the right border was inside the hernial sac, and this was easily reduced. The omentum was removed after a transfixion ligation of its pedicle. The patient developed a mild paralytic ileus, which responded to conservative treatment, and he was discharged on December 11.

FIG. 1.—Case 2. Torsion involving the whole of the great omentum. The actual torsion can be seen at the top of the drawing.

Case 3

A man aged 49 was admitted to Central Middlesex Hospital on November 13, 1944. Two weeks before admission he had colicky abdominal pain followed by pain in the right iliac fossa. This had continued ever since, but had eased considerably before his admission. On November 8 his doctor had noticed a tender lump in the right iliac fossa. He had had appendicectomy five years previously. The bowels were regular and micturition was normal. There was no recent loss of weight.

On examination he was seen to be a well-nourished man with a clean tongue. There was a tender mass in the right iliac fossa below the appendicectomy scar. Temperature, pulse, and respiration were normal. No other abnormality was found in any other system. The following investigations were carried out: culture of a clean specimen of urine grew a scanty growth of *Bact. coli*; occult blood reaction was negative in three consecutive specimens of faeces; the white blood cells numbered 6,500 per c.mm.; a barium enema showed no evidence of organic disease of the colon. No definite diagnosis was made, and laparotomy was thought to be advisable.

Operation.—The abdomen was opened by a low right paramedian incision on November 28. The mass was partially necrotic great omentum, completely separated from its normal attachment, and loosely adherent to the antimesenteric border of the last foot (30 cm.) of the ileum and to the postero-lateral portion of the abdominal wall in

the right iliac fossa; part of it hung down into the pelvis (Fig. 2). It was removed after separating the rather vascular adhesions binding it to the ileum and the posterior abdominal wall. With the exception of slight post-operative chest complications, the patient progressed satisfactorily and was discharged on December 19. Histology of the specimen removed showed necrotic omental fat tissue with vascular thrombosis. In some areas there was evidence of organization and recanalization of the vessels.

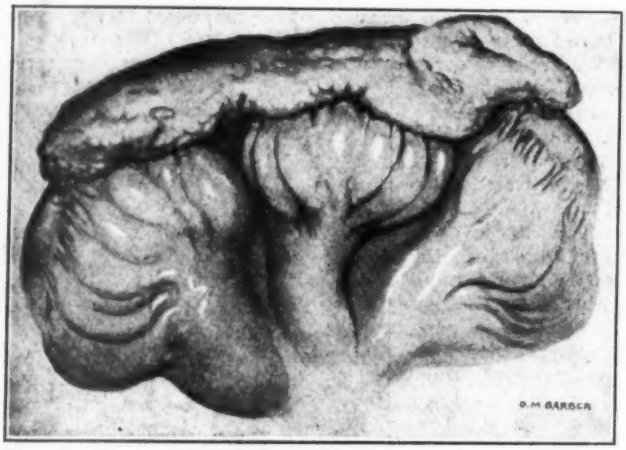

FIG. 2.—Case 3. Partially necrotic great omentum adherent to the antimesenteric border of the ileum.

The operation in this case was performed about a month after the onset of symptoms. It is reasonable to assume that torsion was the cause of complete separation of omentum from its normal attachment; partial revascularization had taken place following its further attachment to the small bowel and postero-lateral abdominal wall.

Comment

The pre-operative diagnosis of torsion is seldom made; about 80% of cases are diagnosed as appendicitis, but, considering the duration of symptoms, the patients look less toxic than do cases of appendicitis. The age incidence varies between 35 and 55 years, and the condition is twice as common in males. The three cases reported here were all those of men between 45 and 50.

Cases 2 and 3 are examples of secondary torsion, the third case being associated with intraperitoneal adhesions, and the second with a right inguinal hernia, though there was no evidence of adhesions between the hernial sac and the omentum. No definite cause was found for torsion in Case 1, which can therefore be grouped as an example of primary or idiopathic torsion.

I wish to thank Mr. T. G. I. James for his advice and for permitting me to publish these cases, which were admitted under his care. My thanks are also due to Miss D. M. Barber and Miss E. D. Hewland, the medical artists, for the drawings.

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SPONTANEOUS PNEUMOTHORAX FROM SECONDARY SARCOMA OF LUNG

BY

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The association of pulmonary metastases with spontaneous pneumothorax is rare, and is not described in such standard textbooks of radiology as those of Twining (1938) and Golden (1941). No recorded case of pneumothorax from secondary carcinoma of the lungs has been found in the recent literature. Thornton and Bigelow (1944) described two cases of spontaneous pneumothorax due to secondary sarcoma of the lung, and Lodmell and Capps (1949) added three further cases. In view of the apparent rarity of the condition, the following case is of interest. It showed bilateral spontaneous pneumothoraces following pulmonary metastases from a leiomyosarcoma of the uterus.

Case Report

A woman aged 51 was admitted to Brompton Hospital on March 19, 1949, for investigation of her chest. She was nulliparous, and her husband had died 15 years earlier from pneumonia. She had spent the past four years in Johannesburg. She had had no relevant previous illnesses, except an operation in May, 1948, when a subtotal hysterectomy had been performed for fibroids. No further details of this operation are available. She had since remained in good health until January, 1949, when she fell ill with an influenza-like illness. A radiograph of the chest revealed a left-sided pneumothorax and scattered rounded opacities in both lung fields; there were also bilateral pleural effusions. A provisional diagnosis of multiple secondary deposits was made and the differential diagnosis of hydatid disease was considered. As her relatives were in England, she was flown home on March 18.

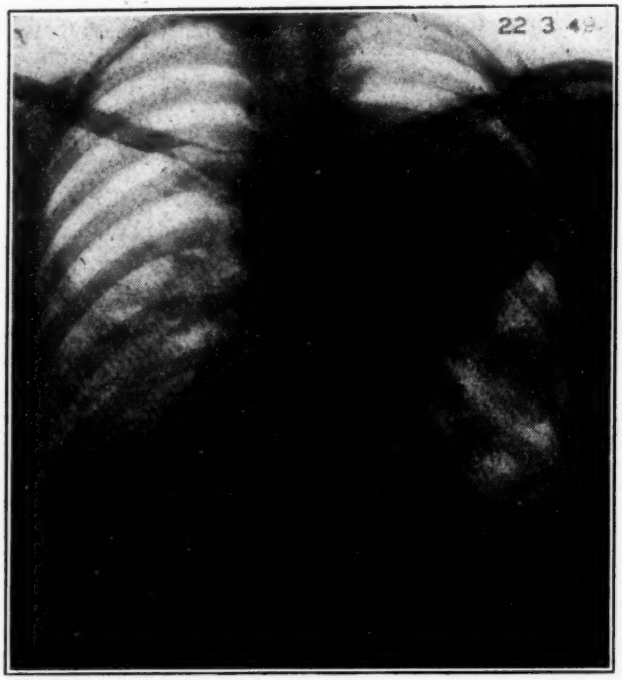
On admission to Brompton Hospital next day she was orthopnoeic and had a temperature of 101° F. (38.3° C.). She had lost a stone (6.4 kg.) in weight since January, 1949, and had coughed up flecks of blood on two recent occasions. Bowel habits and micturition were normal, and there had been no recent vaginal discharge or bleeding.

On examination she was pale and showed signs of loss of weight. She had a remittent fever up to 102° F. (38.9° C.) while in hospital. No enlarged lymph nodes were felt. Air entry was diminished over both lungs, and there was dullness with scattered rales in the left upper and right lower zones. The liver was not palpable, and there was a right lower paramedian scar; vaginal examination revealed a fixed cervix and a firm mass in the right fornix.

Investigations.—The urine contained nothing abnormal. A blood count showed: Hb, 75%; red cells, 3,800,000 per c.mm.; white cells, 12,000 (polymorphs 76%, lymphocytes 8%, monocytes 13%, eosinophils 2%, basophils 1%). E.S.R. (Westergren) 76 mm. in one hour. Repeated examinations of the sputum showed no malignant cells, though in one examination a few clumps of "suspicious cells" were revealed. No tubercle bacilli were seen. The Casoni test (intracutaneous injection of hydatid fluid) was negative.

A chest radiograph on March 22 (see Illustration) showed bilateral pneumothoraces, that on the left side being now localized to the apex. In this region there was a large rounded opacity situated anteriorly, as seen in the lateral view, and a localized hydropneumothorax. Both lung fields showed several rounded shadows. Intravenous pyelography revealed no abnormality.

A punch biopsy was performed on April 6. A Silverman needle (kindly lent by Professor D. W. Smithers) was intro-



Radiograph of chest on March 22, showing bilateral pneumothoraces, that on the left side being localized to the apex. There are multiple rounded opacities in both lung fields, and fluid is present at both bases.

duced into the first left interspace 1¾ in. (4.4 cm.) lateral to the margin of the sternum, and the specimen reported upon as follows: "The material provided is that of a cellular malignant tumour. The tumour cells are very pleomorphic anaplastic cells with large deeply staining nuclei. The material is insufficient for making a definite diagnosis."

The patient was considered unsuitable for radiotherapy, and was therefore given symptomatic treatment only. Her condition slowly deteriorated, with a remittent fever, until her death on April 25.

Necropsy Report (extracted from Brompton Hospital post-mortem register).—The right pleural cavity contained a large pneumothorax with collapse of the upper lobe. The right lung was extensively infiltrated by deposits of tumour, some of which had caused ulceration of the visceral pleura. The left pleural cavity was obliterated except at the apex, where there was a small pneumothorax. Multiple deposits were present throughout the left lung, and a large deposit in the apex of the left upper lobe contained necrotic blood-stained material. The left main bronchus contained a mass of growth, 4 in. (10 cm.) long, lying in the bronchus and arising from a tumour mass in the lingula. In the pelvis the body of the uterus had been removed. The right ovary was replaced by a hard, white, irregular tumour, approximately 3 in. (7.5 cm.) in diameter. The left ovary was cystic and its contents were blood and necrotic tissue. The cervix, vagina, and bladder were normal. There was no macroscopic evidence of secondary deposits in the liver or other organs.

Histology.—"The mass replacing the right ovary is a well-differentiated leiomyosarcoma. Even in this lesion, however, there are areas where the tumour is highly pleomorphic, and other areas show extensive necrosis. The wall of the left ovarian cyst is lined by a zone of pleomorphic tumour. The frond-like mass in the left main bronchus is pleomorphic, contains many giant cells, and shows extensive necrosis. The degree of differentiation of the leiomyosarcoma in the various lung metastases is extremely variable. Some are anaplastic with numerous giant cells, others show almost normal differentiation. Necrosis is widespread."

Comment

The clinical findings and radiological appearances suggested the diagnosis of multiple pulmonary metastases. The differential diagnosis of hydatid disease had been considered in South Africa, for hydatid cysts may produce multiple rounded shadows in the lung fields in association with a pneumothorax. However, the finding of a mass in the pelvis favoured the diagnosis of metastases, and this was confirmed by punch biopsy. The necropsy showed that the pneumothoraces were almost certainly caused by broncho-pleural fistulae arising from necrotic pleural metastases. Partial re-expansion of the left lung had occurred during life, from the growth of the large mass in the left upper lobe.

The histological appearances of the tumours in the ovaries and lungs were those of leiomyosarcoma. It is thought probable that these deposits were secondary to the uterine tumour which had been removed 11 months before the patient's death, and that this was a leiomyosarcoma and not a benign fibroid. Willis (1948) has cited a case in which the interval between hysterectomy for supposedly simple "fibroids" and the development of leiomyosarcomatous metastases in the lungs was almost two years. An adequate histological study will usually reveal whether a uterine fibroid is benign or malignant, and it is a well-recognized experience to find suspiciously sarcomatous areas in a fibroid which is clinically benign (Willis, 1948). Less frequently a tumour may appear benign after careful study, but its malignant nature is proved by its subsequent clinical behaviour (Steiner, 1939). It has not been possible to examine the tumour removed by hysterectomy in the present case, but its malignancy seems to have been proved by the subsequent development of metastases.

Spontaneous pneumothorax may occur in association with a primary bronchial carcinoma, especially in the later stages, when there is secondary abscess formation and tissue gangrene (Young, 1936; *Brit. Ency. med. Pract.*, 1949). A pneumothorax may also result from the local spread of a malignant tumour—for example, oesophagus or heart (Perry, 1939). However, the association of a spontaneous pneumothorax with secondary pulmonary metastases has been recorded only in recent years. Of the two cases described by Thornton and Bigelow (1944) one was due to spread from a fibrosarcoma of the hand that had been amputated five years earlier, and the second followed an amputation of the leg for an osteogenic sarcoma of the femur. In both instances the pneumothoraces were bilateral. Lodmell and Capps (1949) described three further cases. In the first, pulmonary metastases and bilateral pneumothoraces developed one month after a mid-thigh amputation for an osteogenic sarcoma of the tibia, and in the second case the primary growth was an inoperable sarcoma of the neck. The third case was an angiosarcoma of the retroperitoneal space; multiple pulmonary metastases and a spontaneous pneumothorax developed five months after laparotomy.

The mechanism of production of a pneumothorax due to secondary metastases has been discussed by Lodmell and Capps. The most likely explanation is that the pneumothorax is caused by a broncho-pleural fistula following necrosis of a subpleural nodule, and this was probably the method in the present case. Lodmell and Capps, however, failed to demonstrate such a fistula in two of their three cases. They suggested that in these cases the tumour nodules had produced a ball-valve

obstruction of the bronchi, with distension of the peripheral alveoli. These distended alveoli might subsequently rupture direct through the visceral pleura or into the interstitial spaces. In the latter case the air may then track along intrapulmonary tissue planes to the mediastinum, or peripherally to the subpleural surface, when blebs may form and subsequently rupture.

The rare occurrence of spontaneous pneumothorax in association with metastatic tumours of the lung is somewhat surprising, as lung necrosis is a conspicuous feature in such cases, and pleural perforation might be expected more commonly. Certainly few such cases have been recorded.

I wish to thank Dr. Neville Oswald for permission to publish this case. For the reports on the pathological findings I am indebted to Dr. J. W. Clegg.

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HAEMOLYTIC TRANSFUSION REACTION DUE TO AN ANTI-LEWIS^a AGGLUTININ

BY

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AND

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In April, 1950, a blood sample was sent to our laboratory from a woman aged 25. She had been admitted to the surgical department of this hospital, where a cholecystectomy was performed by Professor Dr. I. Boerema. Two hours after the operation she developed a severe shock, which was treated with blood transfusions. The total amount of blood given, from three different donors, was 1,500 ml. During the infusion of the second bottle there was a mild transfusion reaction with chill and a rise of the temperature to 38.7° C. The transfusion, however, was not discontinued, and blood from the third donor was endured without further reactions. Nevertheless this patient showed the typical signs of a haemolytic transfusion reaction—that is, oliguria with haemoglobinuria—but made an uneventful recovery on being treated in the usual way.

A recheck of the patient's and donors' blood was made. Tables I and II show the results of the blood grouping and cross-matching of the patient's serum with

TABLE I.—*Blood Groups*

Patient	..	A_1	.. MN	..	cde
Donor I	..	A_2	.. MN	..	cde
Donor II	..	A_1	.. MM	..	cde

cell suspensions of donors I and II. An Rh or M or N antagonism could be excluded. The patient's serum contained a cold agglutinin which was still active at body temperature. Incomplete antibodies could not be detected by the indirect Coombs test. We could as well exclude an A_1 and A_2 antagonism, the patient's serum reacting with both A_1 and A_2 cell suspensions at different temperatures. Out of 27 cell suspensions six were agglutinated at 37° C. and five at 44° C.—that is, in about 20%.

On the basis of this frequency we excluded the possibility of an antagonism of the systems H, Jobbins, Kell, and Cellano, and thought a Lewis antagonism most probable, for the following reasons: (1) we were able to prove the connexion between the secreting properties of the patient and the intergroup reaction under discussion, the patient being a secretor, the first donor a non-secretor, and the second donor a secretor; and (2) no agglutination occurred if the patient's serum was mixed with saliva of a secretor and red cells of the first donor (saliva inhibition test).

On these observations we felt justified in concluding that it was a haemolytic transfusion reaction due to the presence of an anti-Lewis^a agglutinin. It is therefore the blood of the first donor that must have been responsible for the haemolytic reaction.

Dr. van Loghem kindly controlled the serological examination in his laboratory. He could exclude the factors C^w, S, P, and Duffy as eventual causes of the transfusion complication (Table III). He also compared our serum with a known anti-Lewis^a serum and found identical figures. Hence he could confirm our results.

The occurrence of anti-Lewis^a agglutinins in human sera has been described several times already. However, it seems to be the first time that this antibody has given rise to a haemolytic transfusion reaction.* Fortunately the consequences of this discovery do not seem to be serious from the clinician's point of view. We may easily believe that the frequency of these reactions will be extremely low. Yet the occurrence of even such rare reactions compels us to take the necessary precautionary measures.

*It was learnt from a personal communication that both Mr. I. Dunsford (Sheffield) and Dr. M. M. Pickles (Oxford) saw similar transfusion reactions. Neither case, however, has so far been published.

TABLE II.—*Cross-matching*

		37° C.			Room			3° C.			
		1:1	1:2	1:4	1:1	1:2	1:4	1:1	1:2	1:4	1:8
Serum patient .. × Cells donor I ..	Saline	++	+	±	++	+	±	+++	+++	+	±
	Albumin	+	−								
Serum patient .. × Cells donor II ..	Saline	−	−	−	−	−	−	+	±		
	Albumin	−	−								

TABLE III.—*Blood Groups*

Patient	..	A_1, MNs, Le(a−), cde/cde, C^w−, Duffy+
Donor I	..	A_2, MNS, Le(a+), cde/cde, C^w−, Duffy−
Donor II	..	A_1, MMs, Le(a−), cde/cde, C^w−, Duffy−

The advance of our knowledge of antigens in human blood is a serious hint to transfusion workers not to contemplate blood transfusion as a routine procedure, but as a medical treatment which needs the closest consideration. Though by that means all undesirable reactions cannot be avoided, it may help to lessen their incidence.

We wish to thank Dr. J. J. van Loghem, jun., for controlling our results in his laboratory.

[After submitting this article for publication we became aware of a paper by V. I. Krieger and R. T. Simmons (*Med. J. Aust.*, 1949, **1**, 85), which deals with a similar transfusion reaction.]

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Medical Memoranda

Codeine Sensitivity

In spite of the widespread use of codeine in therapeutics, only 12 cases of idiosyncrasy have been recorded in the literature, including an earlier case I reported (Mackenzie, 1949). However, the similarity between the reaction to codeine and one of the exanthemata makes awareness of the possibility a matter of some clinical importance, especially in view of the increasing tendency of the laity to take codeine compounds for a "cold" or sore throat. Publication of the following two cases therefore seems justified.

Case 1

A motor mechanic took two "veganin" tablets one evening for a "cold." The next morning he noticed an irritation affecting the whole body, and in the evening, 28 hours after taking the tablets, a rash appeared on the trunk and thighs and around the angles of the mouth. Next morning the rash was follicular, with a surrounding erythema; it was most marked over pressure areas, particularly the anterior folds of the axillae, the groins, and the belt area, but was present over most of the trunk and around the left angle of the mouth. He had some general malaise, which he put down to the original "cold." By the next day, without any special therapy, the rash had faded and the irritation lessened, and two days later the rash disappeared, soon followed by the irritation. There remained a fine powdery desquamation, particularly on the anterior folds of the axillae and over the lower face. The patient now felt well. He had never taken veganin before.

The specific nature of the reaction was demonstrated a few weeks later by giving a test dose of codeine phosphate, ¼ gr. (16 mg.) at 3 p.m. Irritation appeared on the lower lip at 7 p.m., and by 9 p.m. had spread to the trunk and thighs. About 11 p.m. a follicular rash appeared all over the body. Both rash and irritation remained through the next day, when a blood count showed 120 eosinophils per c.mm., and on the following day the rash was fading and the more severely affected parts were peeling. Two days later all that remained was some irritation in the belt area and on the thighs. While the rash was present there was general malaise, headache, and nausea. There was no pyrexia throughout, and there were no lesions in the mouth.

Some weeks later the patient was given morphine, ¼ gr.: no reaction of any kind developed. He was then given codeine phosphate, ¼ gr., as a single dose, followed by "benadryl," 50 mg. three times daily. The rash and general symptoms appeared as before, but on this occasion there was practically no irritation.

Case 2

This patient, a girl aged 12, had been given two veganin tablets for a headache and sore throat in the evening. The following morning her body was covered with an irritating rash, which the district nurse reported as scarlet fever. When seen the second morning, the rash was fading, but there was still some irritation present on the chest and arms. Her temperature was 99° F. (37.2° C.). The fauces were inflamed and the tongue was coated. On the following day the rash and irritation had disappeared, leaving only a fine branny scaling.

Further inquiry showed that the patient was not sensitive to aspirin, but she had not previously taken any codeine compounds. Accordingly, two weeks later, when all signs and symptoms had subsided, she was given one tab. codein. co. *B.P.* (codeine content, 8 mg.). Four hours later an itchy macular rash appeared on the face, backs of the hands, and flexures of the knees, spreading in two hours to the chest. Within 24 hours the rash involved the whole body, but was most marked in the waist area and the flexures of the knees. During the next 12 hours the rash faded and the irritation lessened, and in a further 12 hours the rash and irritation had disappeared. There remained only a fine powdery desquamation for a further two days. There was no fever or malaise.

Several weeks later the patient was given a pill containing codeine phosphate, ¼ gr. (8 mg.). A similar reaction followed, and took the same course as already described. Some time after this had subsided she was given a tablet of morphine sulphate, ¼ gr. Four hours later she noticed a slight irritation of the skin, but no rash appeared.

No other member of the family showed any reaction following ingestion of codeine.

Comment

Case 1 differs from the one I previously reported and from Case 2 in that general malaise accompanied the reaction, and the idiosyncrasy was confined to the single opium alkaloid—codeine. In both cases here reported a definite desquamation followed. Neither patient had previously shown any allergic manifestations.

The pruritus and the rash, which may be macular or follicular at the onset, are the features common to all the recorded cases. In addition, some have shown desquamation, eosinophilia, and malaise.

According to the literature, skin tests have been used with varying success to demonstrate codeine sensitivity. In view, however, of the apparent rarity of the condition, their practical value must be limited. As with other suspected drug eruptions, the easiest and best test is the effect of repeating a small dose of the drug.

The literature has been reviewed by Scheer and Keil (1934) and by Seidmann (1943), who also reported further cases.

G. K. MACKENZIE, M.B., Ch.B.

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Seidmann, M. (1943). *Arch. Derm. Syph., Chicago*, **47**, 654.

Prophylactic Proguanil in the Southern Highlands of Tanganyika

The Overseas Food Corporation's training centre at Ifunda, in the Southern Highlands of Tanganyika, situated at an altitude of 5,500 ft. (1,670 metres), was the scene of an outbreak of malaria in 1949. The cases were all of the malignant tertian type, and eight of the patients took proguanil regularly.

The camp, which was originally a Polish refugee camp, is badly sited on a hillside which slopes down to a swamp, the lower edge being scarcely 500 feet (150 metres) from the swamp. The prevailing wind blows from the camp across the swamp, so that it is only when the wind shifts or dies that the mosquitoes which are always present in the swamp gain access to the camp. Both *Anopheles gambiae* and *Anopheles funestus* are found, and occasionally *Anopheles coustani*.

The Poles are reputed to have had a malaria incidence rate of 700–1,000 per annum.

The camp was occupied by the O.F.C. in April, 1948, and the medical staff advised the use of mosquito nets, long trousers, and long sleeves in the evenings, the "flitting" of houses morning and evening, and the taking of prophylactic proguanil, one tablet a day throughout the year. All African quarters were residually sprayed with "gammexane P. 520" monthly, as were ancillaries such as latrines, cookhouses, stores, and so on. D.D.T. residual spraying of their houses was offered to European staff, but, lulled by the absence in the initial period of both mosquitoes and malaria in the camp, most refused the offer.

The second half of 1949 saw a gradual increase in malaria cases, and on investigation in November 39 out of 51 European staff members and their dependants gave blood slides positive for *P. falciparum*. Table I shows the position on November 10.

TABLE I

Parasites	No. of Positive Smears	Children	Adults	Remarks
M.T. rings ++ (6 per field)	2	1 (2 yrs.)	1	Adults not infected at Ifunda
M.T. rings + (1 per field)	9	6 (1–5 yrs.)	3	All adults and 2 children of L.R.
M.T. rings, scanty (1 per 6 fields)	9	3 (1–6 yrs.)	6	4 adults of L.R.
M.T. rings, very scanty	19	1 (14 yrs.)	18	10 adults of L.R. Child born in India
Totals ..	39	11	28	

L.R. = Long residence in Tropics, 3 years or more.

It will be noted (Table II) that, of the 39 persons with positive blood, 16 took proguanil regularly, and 8 of these developed overt malaria. Of the 11 persons with positive blood taking proguanil irregularly, 6 developed overt malaria, and, of 12 persons with positive blood not taking paludrine, 10 developed overt malaria.

Twelve persons gave negative smears on November 10, but 6 of these had had positive smears earlier in the year (Table III).

TABLE III

Negative Bloods	Regular Proguanil		Irregular Proguanil		No Proguanil	
	No.	Overt Malaria, 1949	No.	Overt Malaria, 1949	No.	Overt Malaria, 1949
12	3	2	2	Nil	7	4

Considerable care was taken in checking and cross-checking the stories of regular proguanil-taking. All stories were checked on the evidence of at least one other person, and even those who were known to be proguanil takers, but who admitted to missing one or at the most two doses a week, were put into the irregular class. Of the regular proguanil takers, two were sisters in the camp hospital, one was the doctor, and two were children of the doctor. Another was the health inspector. The symptoms of the disease were mild, whether the persons affected had been taking proguanil regularly, irregularly, or not at all. That is, the symptoms were those commonly occurring in malaria at high altitudes in East Africa.

Attacks or positive blood smears were directly related to the position of the houses occupied, relative to the swamp. The row of European houses next to the swamp, at approximately 500 yards (460 metres), were occupied by 14 persons, and only one of these had a negative blood. The middle row of houses, approximately 700 yards (640 metres) from the swamp, were occupied by seven persons and none were free from the disease. The back row of houses, at approximately 1,100 yards (1,000 metres) from the swamp, were occupied by 31 persons, and six were and had been free from the disease.

Personal precautions had been largely ignored by the inhabitants. The use of nets and of "flitting" was small and most irregular. Residual spraying had been largely refused.

Thanks are due to the chief health officer, Brigadier W. M. Cameron, for permission to publish this article; to Dr. V. Blackman, who is in charge of the O.F.C. Medical Training Wing at Ifunda; to Sisters Puddicombe and Morrison; to Mrs. Franklin, the hospital secretary; and to Mr. Frank Henry, the laboratory technician.

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TABLE II

Parasites	No. of Positive Smears	Regular Proguanil*		Irregular Proguanil		No Proguanil	
		No.	Overt Malaria†	No.	Overt Malaria†	No.	Overt Malaria†
M.T. rings ++.. ..	2	1	—	—	—	1 ad. (L.R.)	1
M.T. rings + ...	9	3 children	3 (2 of L.R.)	1 ad., 1 ch.	Both (ad. of L.R.)	2 ads., 2 ch.	4 (2 ads. of L.R.)
M.T. rings, scanty ..	9	3 children 3 adults	2 ads. (1 of L.R.)	1 ad.	1 ad. of L.R.	2 ads.	2 (1 of L.R.)
M.T. rings, very scanty	19	6 adults‡	3 ads.	8 (7 ads., 1 ch.)	3 ads. (2 of L.R.), 1 ch.	5 ads.	3 (2 of L.R.)
Total	39	16	8	11	6	12	10

* Taking proguanil regularly (1 a day). † Refers to attacks in 1949. ‡ 1 regular since October 4.

Reviews

BERYLLIUM

Pneumoconiosis. Beryllium. Bauxite Fumes. Compensation. Leroy Gardner Memorial Volume. Edited by A. J. Vorwald, M.D., with the collaboration of M. Bowditch, A.B., T. M. Durkan, M.E., and T. C. Waters, LL.B. Sixth Saranac Symposium. (Pp. 659; 196 figures. $7.50.) New York: Paul B. Hoeber, Inc. 1950.

This book is a verbatim report of a symposium held at the Saranac Laboratories, Massachusetts, in the autumn of 1947. It is dedicated to Dr. Leroy Gardner, who contributed so much to the experimental study of silicosis. Just before his death in 1946 he had begun to investigate a disease that had recently appeared among workers in fluorescent-lamp factories where beryllium compounds were handled. The greater part of this volume is devoted to contributions on the nature and incidence of disease among beryllium workers and an account of work on the toxic properties of beryllium as revealed by animal experiments. The concluding sessions discussed a new pulmonary disease due to exposure to bauxite fumes, now known as Shaver's disease in recognition of the man who first described it. The summary of the discussion on Shaver's disease by Dr. Hatch is all that a summary should be. The last section on compensation for occupational disease is of no particular value to English readers, though it makes interesting, and at times amusing, reading. The problems associated with this type of legislation are plentiful enough under the unified code of this country. It does not require much imagination to appreciate the situation in a country where 39 of the States have their own varied laws and any firm may have factories in many different States.

The papers on beryllium occupy three-quarters of the book, and, as might be expected, are of a varied quality. These papers were read three years ago, and much more has come to light since then. There is now little doubt that the chronic pulmonary granulomatosis of beryllium workers is a real clinical entity. At first it appeared among a group of workers exposed to a fluorescent-lamp powder (phosphor) containing 12% beryllium oxide, and the cases occurred in a relatively small working population. Other firms using phosphors containing 2% beryllium oxide reported no cases. Dr. Williams suggested that cases among these workers might take longer to develop. Events have proved him to be right. Indeed, a recent paper suggests that exposure to concentrations as low as 0.1 μg. per cubic metre may be enough to produce the disease. It is not surprising, therefore, to learn now that factories making beryllium are moving out into country areas. The peculiar incidence of the disease remains unexplained. One contributor suggested that beryllium oxide produced under different conditions—for example, heated to different temperatures—might have different biological properties (page 349). He, too, has been proved correct in recently reported experimental work. Particle size and shape are important in determining the toxicity of beryllium oxide.

There seems to be general agreement that the chronic form of the disease among beryllium workers can be recognized clinically, and Dr. Hardy clearly describes its features. The *x*-ray appearances are not by themselves characteristic, and Aub goes so far as to say that he does not consider it necessary that beryllium should be found in the tissues in order to confirm the diagnosis.

Hardy is in a minority in believing the chronic disease is a manifestation of systemic beryllium poisoning rather than a purely pulmonary disorder. There is much to support her contention, though the work of Dr. George Wright indicates that function of the lungs is seriously impaired before there is an appreciable loss of vital capacity. This fails later and aggravates the dyspnoea still further.

The experimental work reported was mostly of a preliminary nature, and much of it has been fully reported elsewhere since the symposium was held. It remains as true to-day as it was in 1947 that it has proved impossible to reproduce the chronic form of the disease in animals. Experimental work has served only to throw what is described in another connexion (page 31) as "black light" on this particular problem.

The volume ends with a bibliography of work on beryllium more or less complete up to the end of 1949. No reason is given for the delay in the appearance of this book, but it is some consolation to know that printing and publishing delays are not confined to a country which has now had five years of "applied Marxism" (page 571) to sap its vitality. One cannot help concluding with a note of regret that a book almost entirely devoted to work on two of the lightest of the elements should be so heavy to hold.

J. M. BARNES.

PRACTICAL ENDOCRINOLOGY

Hormones in Clinical Practice. By H. E. Nieburgs, M.D. (Pp. 388; illustrated. £1 5s.) London: Cassell and Co. 1950.

Professor Nieburgs, of Georgia, who has worked in England at the British Postgraduate School and at the Westminster Hospital, presents in this book a synoptic but informed account of endocrinology from a practical point of view. In a comparatively small volume such as this some sections are bound to be inadequate and even fragmentary. But the book is offered "not as yet another textbook of endocrinology but rather as a work of reference embodying the most recent data on the physiology of the hormones and their use in clinical practice."

In an endeavour to give full references, the author lets them obtrude in a disturbing fashion, interrupting the smooth reading of the text. The latter in itself, however, is open to criticism. A statement without reference and which seems to call for further information and qualification is: "Adrenal cortical atrophy can be produced with progestogen [*sic*] or testosterone if large doses are used." Another statement runs: "Adrenal cortical hyperplasia does not appear to increase the corticosteroid excretion, but it does increase that of 17-ketosteroids." In fact, either hyperplasia or neoplasm of the adrenal cortex can increase either corticosteroids or 17-ketosteroids, separately or together, or in varying proportions. The chapters on gynaecological endocrinology, including accounts of several diagnostic procedures, are based on extensive clinical experience and will be found to constitute a useful guide in practice.

S. LEONARD SIMPSON.

RADIOLOGY IN DENTISTRY

Radiology of the Teeth and Jaws, including Dental Radiography. For Students and Practitioners of Dental Surgery and Radiology. By Frank L. Ingram, D.M.R.D., L.D.S., M.R.C.S., L.R.C.P. (Pp. 160; 281 figures. 16s.) London: Edward Arnold and Co. 1950.

Designed for both students and practitioners of dental surgery, the book is divided into two main parts. The first is on the technique of radiography and includes a description of the normal appearances; the second is mainly devoted to a description of the pathological conditions in which radiography is useful. The book contains many illustrations; while many of these are excellent, some, notably those of the skull, are rather vague, and the definition is not sufficiently good to give a clear picture of the condition, particularly to the student. These criticisms apply especially to the pictures of the mandibular condyle and also to those of the maxilla, and possibly explanatory diagrams by the side of the photographs might have helped.

It would perhaps have been wiser if the author had avoided the temptation to discuss the pathology of the condition in notes underneath the photographs, and he has courted danger in one or two places by giving hints for treatment. This occurs notably in the section on fractures of the mandible, and the danger becomes apparent when it is seen that his suggestions may not be acceptable to all. In spite of these slight drawbacks the book will be helpful, but it is unfortunate that the illustrations are not clearer.

ALEXANDER MACGREGOR.

PHYSICAL MEDICINE

Recent Advances in Physical Medicine. Edited by Francis Bach, M.A., D.M.(Oxon), D.Phys.Med. (Pp. 490; 93 figures. £1 7s. 6d.) London: J. and A. Churchill. 1950.

In the preface to this well-produced book Dr. Bach defines physical medicine as including the employment of the physical and other effective properties of light, heat, cold, water, electricity, massage, manipulation, exercises, and mechanical devices for physical and occupational therapy in the diagnosis and treatment of disease. But it would seem, after reading the book, that even this fairly expansive definition is inadequate to meet the claims of this robust infant specialty. This volume will be of considerable interest to the profession, since it defines for the first time the projected field of the specialist in physical medicine.

Section 1 is on the physical basis of the subject and shows the need for a considerable knowledge of physics, including an understanding of the quantum theory. Chapters follow on anatomy, physiology, posture, and the special patterns of blood supply to muscles. Then comes an excellent section on physical methods of electro-diagnosis and therapy, hydrotherapy, massage, manipulation, remedial exercises, and home and occupational therapy. Section 3 is entitled "The Practice of Physical Medicine"; it includes large portions of the practice of orthopaedics, diseases of the chest, peripheral vascular disease, neuropsychiatry, rheumatology, dermatology, paediatrics, and geriatrics, with chapters also on plastic surgery, local infections, and ophthalmology.

The role of physical medicine as it affects the school child, the Army, and industry are the themes of Section 5, and largely comprise what elsewhere might more commonly be termed "social medicine." The borderline between these specialties is perhaps to be found in Section 6, which is on rehabilitation in industry, rehabilitation in a residential centre, the employment of the disabled, and the resettlement of disabled persons. In the final section are chapters on the training of the doctor and the physiotherapist, followed by appendices on rehabilitation in spinal injuries, post-operative breathing exercises, and postural drainage.

This very wide field of knowledge will in future have to be covered by the physical-medicine specialist. As Dr. Bach states, he is to be a new type of doctor, who "should be characterized not only by his special knowledge of biophysics, and his technical ability to apply this knowledge, but also by the depth of his understanding, the breadth of his interests, and his stature as a physician."

In order to cover this extensive field Dr. Bach has collected a team of 38 collaborators, who contribute chapters on the various subjects mentioned above. Of particular practical interest to the embryo specialist will be Dr. Kersley's chapter on the training for the diploma in physical medicine, since information of this sort will not be found in more ordinary textbooks. This is an interesting and to some extent provocative volume, which will be read with profit by both specialists in physical medicine and medical men in other fields.

W. S. C. COPEMAN.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Modern Trends in Paediatrics. Edited by the late Sir Leonard Parsons, M.D., F.R.S., F.R.C.P. (Pp. 546. 55s.) London: Butterworth. 1951.

How to Help Your Growing Child. By U. Grahl. (Pp. 28. 3s.) London: New Knowledge Books. 1950.

Renal Diseases. By E. T. Bell, M.D. 2nd revised ed. (Pp. 448. 56s.) London: Henry Kimpton. 1950.

The British Encyclopaedia of Medical Practice. Edited by Lord Horder. 2nd ed. Vol 4: Cornea, Injuries and Diseases, to Ear Diseases. (Pp. 688. 60s. per vol.) London: Butterworth. 1950.

The Science of Heredity. By J. S. D. Bacon, M.A., Ph.D (Pp. 192. 3s. 6d.) London: Watts. 1951.

Vile Repose. By M. P. O'Connor. (Pp. 302. 9s. 6d.) London: Ernest Benn. 1950.

Regional Orthopedic Surgery. By P. C. Colonna, M.D. (Pp. 706. 57s. 6d.) London: W. B. Saunders. 1950.

English-German Medical Dictionary. Compiled by F. S. Schoenewald, M.D. (Pp. 242. 35s.) London: H. K. Lewis 1951.

Bronchoesophagology. By Chevalier Jackson, M.D., Sc.D., LL.D., F.A.C.S., and Chevalier L. Jackson, M.D., M.Sc., F.A.C.S. (Pp. 366. 63s.) London: W. B. Saunders. 1950.

Psychosomatics and Suggestion Therapy in Dentistry. By J. Stolzenberg, D.D.S. (Pp. 152. $3.75.) New York: Philosophical Library. 1950.

I Vizi della Mitrale. By A. Luciani. (Pp. 157. $3.50.) Pisa: Omnia Medica. 1950.

Exotische Krankheiten und Krankheitsverläufe. By F. O. Höring, M.D. (Pp. 407. M. 36.) Stuttgart: Georg Thieme. 1950.

Therapie des Diabetes Mellitus. By Dr. G. R. Constam. (Pp. 291. 16.50 francs.) Basle: Benno Schwabe. 1950.

Ärztliche Weltanschauung. By Dr. H. Schwarz. (Pp. 213. Sch. 64.) Vienna: Wilhelm Maudrich. 1951.

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DISEASES OF MALADAPTATION

In the present number of the *Journal* Professor Hans Selye adds another stimulating paper to the series which has already appeared in these columns.[1-3] In the first paper he outlined his theory of the general adaptation syndrome and explained his views on the aetiology of a wide variety of medical disorders of hitherto uncertain cause. In Selye's view these are due to an excessive secretion of the mineralo-corticoid hormones of the adrenal, in contrast to the glycogenic hormone of the same gland. By injection of the synthetic mineralo-corticoid, desoxycorticosterone, into rats previously made more sensitive to the drug by unilateral nephrectomy and a high salt diet, he has been able to produce experimental lesions closely similar to, if not identical with, such human disorders as myocarditis, nephrosclerosis, and periarteritis nodosa. But there is a widely held belief that desoxycorticosterone is not a naturally occurring product of the adrenal gland, and this was a weak point in his argument. To meet this criticism Selye[2] showed that identical lesions could be produced in rats by injecting another steroid, desoxocortisone (Reichstein's compound S), which is more generally acknowledged to be a naturally occurring substance. Apparently identical lesions have been observed after injections of crude anterior pituitary extracts. When a traumatic periarthritis is induced in rats by injection of formalin into the region of the ankle, the resultant swelling is aggravated by giving either desoxycorticosterone or a crude anterior pituitary extract. This action, however, can be almost completely antagonized by cortisone or by A.C.T.H. It should be said here that Professor Selye has given up the use of formalin in these experiments, and therefore it probably did not turn out to be the experimental weapon he was in need of.

In the paper in this issue Professor Selye now shows that when somatotrophic hormone—the growth hormone of the pituitary gland—is injected into rats made sensitive, as in earlier work, by unilateral nephrectomy and excess of salt in their drinking-water, then the same series of pathological lesions develops. Malignant nephrosclerosis with varying degrees of nephritis, myocarditis, periarteritis nodosa, and hypertension have all been produced in this manner. Selye attempts to fit these new results into his general concept of the aetiology of these diseases. The somatotrophic hormone which he used was shown to be pure by electrophoresis, yet it caused the lesions in the kidney and in the cardiovascular system. The simultaneous injection of this same pure hormone aggravated a periarthritis produced experimentally by injections of a 10% suspension of mustard powder in the same way as desoxycorticosterone aggravated the formalin periarthritis. Selye postulates, therefore, that the somatotrophic hormone may sensitize the tissues to mineralocorticoids like desoxycorticosterone, and further that it may even increase the secretion of mineralo-corticoids by the adrenal glands. He offers much experimental evidence to support his views. It is doubtful, however, whether the data support Selye's hypothesis more than they do possible alternative theories.

As one reads the present paper the suspicion tends to grow that the effects he so frequently obtains may be those of a non-specific allergic reaction to foreign substances. This explanation has been suggested before, but Selye felt that the fact that the naturally occurring desoxocortisone also causes the lesions made this explanation very unlikely. Selye himself has now produced the varied lesions he describes with two different steroids and two different proteins. They have been induced by crude anterior pituitary extract, which presumably contains A.C.T.H., but are inhibited by purified A.C.T.H. They are now found to be caused by growth hormone as well. It is difficult to avoid the conclusion that these substances have a common factor determining ability to induce the lesions, and that this common factor is likely to be the ability of the injected substance to evoke some form of allergic reaction. So little is at present known about desoxocortisone that it is scarcely justifiable to rule out the possibility of its causing allergic reactions also, even though it is a natural product. As these thoughts grow in the mind and as the suspicion is strengthened that somatotrophic hormone may be a non-specific irritant or antigen to the tissues, there is naturally a temptation to attach greater significance than does Professor Selye to some further observations which he reports in this paper. He finds that when this pure somatotrophic hormone is injected into the ankle-joint region of rats it causes an extensive granulomatous reaction in the periarticular structures. This protein, though electrophoretically pure, must therefore be acting locally as a foreign irritant. It apparently gives rise to the same effects as do formalin and mustard.

1 *British Medical Journal*, 1949, 2, 1129.
2 Ibid., 1950, 1, 203.
3 Ibid., 1950, 1, 1383.
4 *Stress*, 1950, Montreal.
5 *British Medical Journal*, 1950, 1, 1362.

Professor Selye, whose book on stress[4] has recently been published, was in Britain last year to give the Heberden Oration.[3 5] In this he recalled his early experiments on some effects of ovarian extracts. He described how, because he obtained certain effects which other workers could not confirm, the idea of a non-specific impurity arose in his mind and prompted him to try to bring about the same effects with another substance deliberately chosen at random. The substance he chose was the laboratory bottle of formalin. It was the common effects which were produced by these and a variety of other substances which led him to postulate the general adaptation syndrome to stress. If now somatotrophic hormone, when injected into the ankle, produces a periarthritic granuloma similar to that caused by formalin, then the probability clearly arises that somatotrophic hormone, in addition to its physiological actions, behaves also as a non-specific stress or irritant. Until this strong probability can be eliminated it is clearly unsafe to regard as specific its effects, which may be largely non-specific. Selye suggests, for instance, that the variable cortisone requirements of individuals may be largely determined by variable growth-hormone secretion. But all the scanty evidence so far available suggests that cortisone requirements vary with the severity of the stress, whatever may be the cause of that stress.

Selye finds that unilateral nephrectomy sensitizes his rats to these steroid and hormone injections. It is difficult to see how removal of one kidney can appreciably alter the hormone concentrations surrounding the other tissues of the body. But removal of one kidney will double the amount of toxic products which must be excreted by the remaining kidney. Furthermore, the operation itself constitutes a general stress, the effects of which may augment the later stresses caused by toxic hormone injections. The whole problem is full of obscurities, and alternative explanations of Professor Selye's results are likely to persist until much more experimental work has been done to separate out specific physiological effects from those of a non-specific nature. That cortisone will inhibit these effects does not clarify the picture, for cortisone will inhibit a large variety of pathological processes of widely different primary cause. And, although the mode of action of cortisone is not yet understood, it is surely not yet justifiable to conclude, as does Selye, that it acts solely by depressing A.C.T.H. secretion by the pituitary. Many who attempt to follow Selye's reasoning from his experiments will feel that his may not be the only deductions that can logically be made.

IMPORTANCE OF RARE BLOOD GROUPS

Apart from the subgroups of the ABO system and the relationship of H thereto, many variations within the established blood-group systems have been described. S has joined M and N; C^w, C^u, c^v, D^u, and E^u have been added to the Rh system; Kell, Lutheran, and Duffy have arisen as newly defined and fairly straightforward groups, and finally the interesting and complex Lewis system is under investigation. Still further groups are known, but because of the rarity of their occurrence, or because they are not yet sufficiently well defined, they are of less consequence. These new groups are important for the practice of medicine as well as extremely interesting to serologists, geneticists, and ethnologists. The mechanisms by which they may cause disease are similar to those which operate in the common Rh system. During blood transfusion, for example, antibodies to the rare groups may cause a haemolytic reaction. Coombs, Ikin, Mourant, and Plaut,[1] in reviewing the occurrence of anti-S, mention one case in which this antibody probably caused transfusion reactions, and de Vries and Smitskamp elsewhere in this issue of the *Journal* report a transfusion reaction due to anti-Lewis (anti-Le^a); the Kell and Duffy groups have been incriminated similarly.

In view of the multiplicity of blood groups it is surprising that reactions from rare blood-group incompatibilities are not more common. One explanation of their rarity is that these blood groups fortunately appear to be poor antigens. Put differently, the majority of human subjects do not make isoantibodies to a dangerous degree against the lesser-known red-cell antigens. Four reported examples (one in last week's *Journal*) of an unusually sensitive antibody-producing capacity throw this normal passivity into relief.[2-5]

At present it is not easy to detect those few who are likely to produce blood-group antibodies to a dangerous degree, for there is no reason to assume that capacity to produce antibodies against one type of antigen (for example, bacterial vaccines) will run parallel with the response to other antigens such as those of the blood groups.[6] Further work on these lines might be profitable. However, the report of

1 *British Medical Journal*, 1951, **1**, 109.
2 Waller, R. K., and Race, R. R., ibid., 1951, **1**, 225.
3 Callender, S. T., and Race, R. R., *Ann. Eugen., Camb.*, 1946, **13**, 102.
4 Collins, J. O., Sanger, R., Allen, F. H., and Race, R. R., *British Medical Journal*, 1950, **1**, 1297.
5 Malone, R. H., and Cowen, J., ibid., 1950, **1**, 1299.
6 Carlinfanti, E., and Cavalli, L. L., *Revista dell' Instituto Sieroterapico Italiano*, 1947, **22**, 129.
7 Paper read at the Third International Congress of Haematology, Cambridge, 1950.
8 *Lancet*, 1951, **1**, 150.
9 Ibid., 1951, **1**, 204.
10 *Blood Groups in Man*, 1950. Oxford.

Coombs and his colleagues shows that antibodies against the rarer groups may occur spontaneously; the anti-S which they describe does not appear to have been produced by immunization. These observations, and the fact that the rarer groups may be concerned in haemolytic disease of the newborn (C^w and Kell have been incriminated), are further reasons why indiscriminate transfusions should be avoided.

For the pathologist bed-side cross-matching is no longer adequate, for experience with Rh problems has shown that compatibility tests require skilful handling and the use of laboratory equipment. The use of albumin media is essential to exclude incomplete forms of antibody, and for the D^u and Duffy groups only the anti-globulin technique will suffice. Furthermore, the possible complication of the "cold incomplete auto-agglutinins" described by Dacie[7] must be borne in mind. There may be occasions when, to make certain of compatibility or to investigate a transfusion reaction, assistance will be required from a specialized laboratory where rare sera and cells of unusual genotypes will be available. Reference of irregular or unexplained results to such a laboratory may also add to our knowledge of the existing systems or disclose new ones.

The rarer antigens have their purposes, however. It may soon be possible to use the blood group antigens as gene markers on the chromosomes. The discovery of a relationship between the Le^a antigen and the power to secrete the ABO substances is a first step in this study, and James and Plaut[8] suggest that the inheritance of the power to make Duffy antibodies (anti-Fy^a) in haemophiliacs might be investigated. The use of the rarer groups in identification tests renders the conclusions more reliable. This method of confirming that twins are uniovular may help in studying congenital disorders, and Milne[9] was able to make use of S, P, Lewis, and Lutheran in this way.

Evidence based on the known blood-group systems could now be given with even more sureness in paternity cases, if asked for. Race and Sanger[10] estimated that, equipped with suitable antisera from six systems and using "secretor" capacity, about 62% of Englishmen wrongly accused of paternity could be exonerated. There is no doubt about the validity of blood-group tests in matters of paternity or identification. The scientific limiting factors are the supply of sera and the experience of the laboratory worker concerned, and, as these increase and the discovery of new groups proceeds, an increasingly large number of men will be in a position to establish their innocence. It is to be hoped that they will have the opportunity.

THE BRONCHIAL VESSELS

The anatomy of the bronchial arteries and veins, and their relation to the pulmonary vessels in health and disease, have in recent years excited interest and some controversy. Marchand, Gilroy, and Wilson,[1] of Johannesburg, have lately published their investigations, based on injections. Some specimens were dissected after injecting the vessels with variously coloured plastics; stereoscopic radiographs were taken of others after injection of radio-opaque suspensions, the particles of which were just too big to enter capillaries.

The bronchial arteries commonly arise from the arch of the aorta, just distal to the left subclavian artery. There are usually one or two arteries to each lung. As with arteries of corresponding size elsewhere in the body, variations are common. They have been described by Cauldwell, Siekert, Lininger, and Anson,[2] whose work was based on gross dissections of cadavers. The vessels, especially on the right, may originate from intercostal arteries or, less often, from the subclavian or internal mammary arteries. There may be a common origin for the right and left arteries. In the usual pattern the arteries make an acute angle with the aorta, passing upwards to join the posterior surfaces of the main bronchi, which they then follow, giving branches to all the segmental divisions. In addition to the main artery, there are lesser branches from the whole length of the thoracic part of the aorta; one of these, passing in the pulmonary ligament, may cause bleeding during a lobectomy operation; other small vessels also supply the pleura. The bronchial arteries at first lie between the invaginated layers of the pleura; later they form a network round the segmental bronchi, and also, as described by Snow Miller in his classical monograph,[3] a submucous plexus. Branches supply the lymph nodes and the vasa vasorum of the pulmonary arteries. Tortuous radicles form anastomoses with small pulmonary arteries. These anastomoses, whose existence was formerly denied, are numerous; they have also recently been demonstrated by Cockett and Vass.[4] They are present in the foetus, whose bronchial arteries are of relatively large calibre, and provide the alveoli with an adequate oxygenated blood supply.

The bronchial veins form two separate systems. The deep or true bronchial veins, which communicate freely with the pulmonary veins, start as a network around the intrapulmonary bronchioles and coalesce to longitudinal channels and finally to a single trunk which ends in the left atrium or a main pulmonary vein. The pleuro-hilar veins also communicate with the pulmonary veins, but end in the azygos, hemiazygos, or other systemic veins. They drain the extrapulmonary bronchi, the hilar lymph glands, and much of the visceral pleura.

The Johannesburg authors also describe changes in certain diseases. In inflammatory conditions, such as bronchiectasis, the number of anastomoses between bronchial and pulmonary arteries is increased. In a lung abscess the abscess area is supplied by the bronchial

[1] *Thorax*, 1950, **5**, 207.
[2] *Surg. Gynec. Obstet.*, 1948, **86**, 395.
[3] *The Lung*, 1947, 2nd ed., Springfield.
[4] *Brit. J. Surg.*, 1950, **38**, 97.

artery and not by branches of the pulmonary artery. In emphysema anastomoses are also conspicuous, and the bronchial veins are hypertrophied. Although greatly increased in number, the anastomoses in disease are apparently identical in form with those normally present, and probably result from dilatation of pre-existing channels to facilitate a redistribution of blood flow. Functioning of such anastomoses allows an adequate pulmonary blood supply in many cases of congenital pulmonary stenosis; in patients with Fallot's tetralogy greatly enlarged bronchial arteries are often seen. The connecting vessels from the bronchial arteries to the anastomoses have notably muscular walls, and are probably under vasomotor control. Certainly the bronchial arterial supply can take over from the pulmonary, and the connecting vessels may also act as a buffer to prevent pulmonary hypertension, thereby providing some degree of hydrostatic control. The anastomoses on the venous side also have some function in disease: in mitral stenosis, for example, the raised pulmonary venous pressure is to some extent lowered via these shunts to the systemic veins. Further studies of the bronchial vessels can be expected to lead to more information about the distribution of blood flow in the lung both in physiological and in pathological states.

CORTISONE BY MOUTH

One of the practical difficulties of "cortisone" treatment up to date has been the necessity for a bulky injection, either every day or several times a week, and abscesses have occurred as a result in some cases. When Dr. Philip Hench was in this country last autumn he mentioned that both at the Mayo Clinic and in New York excellent preliminary results have been obtained with cortisone given by mouth in tablet form.[1] Since then two publications have appeared with more details of this method of administration. Freyberg and his associates[2] report on four patients with rheumatoid arthritis treated with oral cortisone acetate, in the form of 100-mg. tablets, the dosage being the same as that commonly used for intramuscular injection. In all respects the clinical effects of orally administered cortisone were comparable to those of this hormone and of A.C.T.H. given parenterally. Two of the patients considered the action was smoother when the drug was given by mouth. Recently Boland and Headley[3] from Los Angeles have reported the results observed in a series of 23 patients suffering from rheumatoid arthritis. They used the oral route with success, both for initial and for maintenance doses, and have compared the quantity necessary to maintain suppression of the disease by the two methods of administration. Although no constant dosage ratio could be established, it was apparent that larger doses, ranging from one-fifth to one-third more, may be needed when the hormone is given by mouth. Only one patient in the series failed to respond to oral cortisone. When this method was tried in the initial suppressive treatment the response was, if anything, more rapid than with the injections, suggesting that cortisone may be absorbed more quickly by the intestinal tract than from injected crystals. This is surprising, for it might be expected that since cortisone is a steroid hormone there would be some inactivation by the liver. It will probably be some time before the tablets are commercially available even in the U.S.A., but these preliminary results are of the greatest interest both to physicians and to sufferers from rheumatoid arthritis. However, there is clearly a risk of overdosage if the patient can raise the dose at will by means of a few extra tablets. In the Los Angeles series there were no side-effects save slight facial hypertrichosis in one case, but the period of observation was too short for any dogmatic statement about the dangers of oral cortisone. It seems possible that this method of administration may be used widely in the future, and this will put a greater onus on the physician both to impress on the patient the danger of overdosage and to be on the alert for early signs of this.

As work with cortisone has developed the need has become more pressing for a satisfactory test to detect and assay cortisone-like steroids in body fluids, particularly the urine. Elsewhere in this issue Dr. C. L. Cope gives a preliminary description of a promising test which depends on the ability of cortisone (compound E) and compound F to reduce the number of circulating eosinophils in the blood. Adrenalectomized mice were used as test animals, and cortisone-like activity has been found to a moderate extent in normal urine and to a greater extent in the urine of women in the late stages of pregnancy and in the urine of a patient with an adrenal cortical carcinoma.

SMALLPOX

In recent years three outbreaks of smallpox in Britain have been started by infected people entering the country from abroad. In 1942 a ship arrived at Glasgow with smallpox cases on board. Infection spread first to the city and thence to the country generally, cases occurring as far from Glasgow as London and Swindon. In all, 25 deaths from smallpox were registered in Scotland in 1942. At the beginning of last year another seaborne case caused an outbreak in Glasgow, and at the end of the year an air traveller started an outbreak in Brighton. These two epidemics have several features in common. They both originated with a well-vaccinated person who had such a modified attack that the disease escaped diagnosis. In the Glasgow outbreak an Asian seaman admitted to hospital with pneumonia on March 10, 1950, developed a sparse eruption four days later which was diagnosed as chicken-pox. The patient made a good recovery and was discharged from hospital nine days later. On March 26 three cases of smallpox occurred in the hospital. In Brighton an R.A.F. officer had a highly modified attack of smallpox which was missed. He infected another occupant of the same house—a young woman. She was removed to hospital, but smallpox was not diagnosed for a further 10 days. The fatality rate in both outbreaks was high: 6 of the

[1] *Proc. R. Soc. Med.*, 1950, **43**, 769.
[2] *Science*, 1950, **112**, 429.
[3] *J. Amer. med. Ass.*, 1951, **145**, 8.

18 confirmed cases in Glasgow and 10 of the 29 patients in Brighton died.

A disquieting feature of both outbreaks was the relatively large toll taken of the nursing staff. In Glasgow eight nurses, one laundrymaid, and one doctor were infected, and another doctor was probably infected; the other cases were six patients in, and one visitor to, the hospital. In Brighton nine nurses, two domestics, and the hospital gardener were victims, two members of the telephone exchange where the second patient worked, and six workers in the laundry where the clothes of the original patient were sent at a time when he was still infectious. Infection of laundry workers by clothes also occurred in the large outbreak of a minor form of smallpox in London in the late 'twenties. In the last Glasgow outbreak only two patients, the original case and a hospital sister, had been successfully vaccinated in recent years. Five of the other seven nurses were thought to have been vaccinated in infancy, and the other two had recently been unsuccessfully vaccinated as well as having been vaccinated in infancy. Three of the patients who died, including the doctor, had never been vaccinated, and the other three had been unsuccessfully vaccinated in infancy: one of these last had had three unsuccessful vaccinations in 1949 and 1950. In Brighton 17 of the 29 patients had never been vaccinated before exposure to infection, and the remainder had been vaccinated in infancy; one of those vaccinated in infancy had been revaccinated in 1946 and another in 1935. Seven of the patients who died had never been vaccinated, and three had been vaccinated in infancy over 50 years earlier. Persons with a record of successful infant vaccination fared better than the unvaccinated in both outbreaks: in Glasgow the six persons without vaccination scars all died, while in Brighton seven deaths occurred among 18 unvaccinated persons and three deaths among 11 persons with a history of infant vaccination.

It is obvious that despite strict control at the air and sea ports it is possible that infectious disease in a passenger may go unrecognized. A modified attack of smallpox which occurs in a well-vaccinated person may be extremely difficult to diagnose, and consequently all illness in persons who have just come from areas where smallpox is endemic should be regarded with suspicion. It is essential that the nursing staffs of hospitals should be protected by effective vaccination. Unfortunately doctors also may become casual about vaccination: besides the unfortunate D.P.H. student in last year's Glasgow outbreak, an unvaccinated medical officer contracted smallpox after visiting the ship in which the 1942 outbreak originated.

We can regard it as fortunate that these recent outbreaks have been limited, for they all contained the elements necessary for a widespread epidemic, and no doubt the country owes much to the painstaking work of public health departments. With the great increase in air travel there is every likelihood of smallpox ceasing to be a very rare cause of death in this country, and both medical officers of health and general practitioners must continue to be on their guard against this disease. The need for infant vaccination remains as great as ever.

THROMBOPHLEBITIS

Thrombophlebitis may be a convenient title for a mixed group of conditions characterized by venous thrombosis, but it has to be remembered that inflammatory changes in the vein walls are only seldom demonstrated. A recent discussion on this subject at the Royal Society of Medicine, ranging over many aspects of thrombo-embolic disease, is reported at page 294. Although thrombophlebitis is quite a common disease and one on which it might be reasonable to expect reliable statistical guidance, it is unfortunately true to say that few medical subjects are so beset with controversy. The literature has innumerable figures but few valid statistics. Further progress depends on much more thoughtfully planned research: information is required on the aetiology, the pathology, and the results of treatment of this disease.

Professor W. Melville Arnott, in opening the discussion at the R.S.M., said that few disorders illustrated so well the general principle that aetiology is rarely single. This was similarly expressed by Aschoff some years ago when he said, "Thrombosis is the function of a number of variables." These variables can be discussed under the traditional headings of changes in the vessel wall, changes in the blood, and changes in the blood flow. As already noted histological changes in the vein walls are uncommon, and this is so even in relatively advanced and long-standing cases. The fact that many cases of thrombophlebitis, in contradistinction to phlebothrombosis, are relieved by paravertebral block supports Ochsner's view[1] that superadded spasm is the main difference between these cases and the more bland examples of venous thrombosis. A truly inflammatory and apparently distinctive tropical phlebitis has been described by Gelfand and others,[2 3 4] but true phlebitis of the deep veins is not often seen in this country. Apart from organic changes in the vessel walls, Professor K. J. Franklin mentioned in the same discussion the possible aetiological importance of venous spasm, functional changes in the endothelium, and the influence of vasotropic factors, but on all these points further research is required. Professor Franklin's contention is certainly correct that only a specialist can now speak with any authority on possible blood changes in this condition. Quick[5 6 7] and others have added new concepts to the theory of blood clotting, but these have not as yet increased our understanding of thrombosis. From time to time hopes have been entertained that a useful diagnostic test might emerge from this work, but so far this has not happened. Lastly there is the blood flow itself. Stasis is certainly not the most important factor in causing thrombosis, but there is little doubt of the part it plays in determining the sites at which thrombosis commonly occurs. Some still

1 Ochsner, A., and de Bakey, M. E., *J. Amer. med. Ass.*, 1940, **114**, 117.
2 Gelfand, M., *Trans. R. Soc. trop. Med. Hyg.*, 1950, **43**, 369.
3 Fisher, A. C., *S. Afr. med. J.*, 1941, **15**, 131.
4 Manson-Bahr, P. E. C., and Charters, A. D., *Lancet*, 1946, **2**, 333.
5 Quick, A. J., *Surg. Gynec. Obstet.*, 1950, **91**, 296.
6 Quick, A. J., and Favre-Gilly, J. E., *Amer. J. Physiol.*, 1949, **158**, 387.
7 Quick, A. J., and Stefanini, M., *J. Lab. clin. Med.*, 1949, **34**, 1203.
8 Blodgett, J. B., and Beattie, E. J., *Surg. Gynec. Obstet.*, 1946, **82**, 485.
9 Leading article in *British Medical Journal*, 1948, **2**, 1026.
10 Evans, J. A., and Boller, R. J., *New Engl. J. Med.*, 1947, **236**, 392.
11 Wright, H. P., Osborn, S. B., and Edmonds, D. G., *Lancet*, 1951, **1**, 22.
12 Murley, R. S., *Ann. R. Coll. Surg. Engl.*, 1950, **6**, 283.

question the value of early post-operative ambulation in preventing thrombosis,[8] but there is increasing evidence of its usefulness,[9,10] and Payling Wright's work has shown the beneficial effects of ambulation on the venous return from the legs.[11]

Considering the abundant material available, it is remarkable how little is known about the changes which occur in ageing thrombi, or about the effects of anticoagulant drugs on their mode of disintegration and final disposal. What are the minimum and optimum periods of anticoagulant therapy? How long should the patient remain in bed? How soon does a "waving" thrombus become safe, how soon is it disposed of, and how much should this influence our views on active movements and ambulation? These are but a few of the questions which need answering. One of Professor A. M. Boyd's main contributions has been a detailed study of the late effects of thrombosis, and to some it will be disappointing that he should confess to finding little use for the anticoagulant drugs. The fact that few cases of thrombosis are characterized by vasospasm makes it difficult to justify the routine use of paravertebral block: technically the procedure is not easy, and it can be an unpleasant experience for the patient, though this is not to deny its very real value in cases of painful white leg with well-marked vasospasm. If it is true, as Professor Boyd declared, that few cases are treated before the third or fourth day of the disease, this is indeed a sad reflection on standards of diagnosis, though without doubt there are many hospitals where careful organization and training have improved diagnosis and thereby treatment. There is certainly a need for a clearer appreciation of the aims of treatment. The main preoccupation must be the protection of the legs from the serious sequelae of thrombosis. The prevention of embolism is highly desirable, but it is not such a dangerous hazard as some have suggested; and Murley has shown[12] that cases of pulmonary embolism will still occur even with the most careful regime. Even so, this does not justify the widespread use of vein ligation recommended by the Boston school.

NO POLICY FOR CHARITY

In a hurried half-hour's debate on May 28, 1946 (when an amendment to Clause 7 of the National Health Service Bill was being debated), the House of Commons voted away by 27 to 14 a man's right to retain some control over his covenanted charity. When he signs a seven-year covenant to pay money to a charitable organization he agrees to give to a specific body which has a specific purpose, and this body cannot legally use his money for some other end—for instance, as a donation to another charity—without obtaining his permission, and the charity commissioners or a High Court Judge or Parliament itself must authorize the change. But in the case of gifts to hospitals, by a few words tucked away in a vast Act, Parliament has indeed altered certain covenants. The money paid annually by deed of covenant signed with some voluntary hospital in the bad old days now passes not to that hospital but to the central Hospital Endowments Fund of the Ministry of Health; and the Minister has recently found it necessary to send out a letter (see p. 308) reminding those who signed these covenants that they are still legally bound to pay up. Not unnaturally this has caused resentment: it has the appearance of an extra tax imposed selectively on those who give alms, a mean trick by the Treasury to make the better-off private individual pay for the National Health Service.

The Hospital Endowments Fund, however, is a kind of pocket money, as Mr. Bevan described it,[1] shared out by all hospitals, whether formerly voluntary or not, on the basis of number of beds and the requirements of their district. It is used to supplement normal State support by the provision of various luxuries such as prizes for nurses[2] and other special local satisfactions for which expenditure has not been officially authorized by the Minister. The Fund was invented as an administratively convenient way of handling in one office all the many charitable endowments of the country's hospitals, and then spreading the resultant pocket money so that even those who had hitherto had none could now get a share. Mr. Bevan apparently had no belief in charity, and it is clear from the record of the debate[1] that he regarded its continuation as of no importance and expected it to die when the Health Service got under way.

However, the charitable individual still seems to have a function. He can still make gifts or bequests to specific hospitals inside the Service, and last year the King Edward's Hospital Fund thought fit to give these hospitals nearly £20,000.[3] In the light of all this the Minister's letter is particularly ill-advised, a tax-collector's demand instead of a friendly request. At the very least it might have enclosed some report showing on what the money had been spent—as any private charitable organization would have had enough imagination to do—so that people might know that, though their gift was not going to the intended recipient, it was at least being charitably spent. Indeed, the Ministry ought to issue a detailed public statement to reassure us that the money is going to charitable projects.

As so often in recent years, the trouble is at bottom due to official insensitiveness to real life and behaviour. A man may grumble if his gift to help a friend is used to relieve the distress of another person he has never met, but he consoles himself with the thought that, though the personal feeling is lost, at least he has helped somebody. What he will not stand for, and rightly, is the swallowing up of his gift by a machine, the loss of both personal contact and the satisfaction of having helped. The sooner the Minister and his officers learn these elementary psychological facts the better. They should make it publicly clear that the individual can still contribute to hospital welfare in a number of ways, and that this aid is welcome. And, having blundered badly, they should apologize by offering to release anyone who so desires from the remainder of his covenant.

1 May 23, 1946. *Hansard*, p. 271.
2 *British Medical Journal*, 1950, 2, 406.
3 Ibid., 1951, 1, 201.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

OBESITY

BY

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Obesity presents social as well as physical dangers. For the first of these we are consulted largely by women. Anxious mothers bring their young daughters bulging with puppy fat derived from a free flow of buns, sweets, and other carbohydrate foods. Puberty is perhaps delayed and the parents have no doubt that it is "a question of glands." Treatment is demanded but seldom necessary. As the endocrine glands adjust themselves to the change from girlhood to womanhood. so one finds the previous rotundity giving place to the elegant figure of complete femininity. The direct influence of hormones on the loss of fat is probably negligible; it is the indirect effect which is important, in that the girl's interests change direction and her desire to be attractive leads automatically to wise eating.

If corpulence persists into late adolescence the problem is more serious. By this time we have a young woman who recognizes that she is different from the others, that for her the parties and dances she attends will but emphasize her unattractiveness and produce profound depression only thinly veiled by the forced gaiety of the rotund.

The married woman who has "run to fat" after several pregnancies is assailed with fears that she will lose her attractiveness and thus her husband.

It is not often that men complain of fatness on social grounds, partly because fat young men are rare compared with women and partly because, once married, their wives practise the age-old tradition of furthering their corpulence by overfeeding. A "comfortably" obese male is alleged to be easier to live with and less likely to stray from the path of virtue.

The physical drawbacks of obesity increase in importance with age. That the expectation of life is shortened by corpulence is reflected in all insurance companies' figures. It is not so much a question of being over weight for a given height as of the abnormal distribution of excess weight. The belly measurement catches up the chest circumference, then passes it, and within a year or two that ominous bulge which hides the feet from the victim's eyes presents a signal which if disregarded may spell disaster. The increased risks to the obese of post-operative embolism and pulmonary collapse, of diabetes, hypertension, osteoarthritis, bronchitis, and various skin diseases, are well known and need no elaboration. The strain on an ageing heart even if unaffected by disease must be considerable. If a patient be resistant to a suggestion of dietetic restriction it is not a bad plan to ask him how he would feel if he carried with him all day a suitcase weighing 56 lb. (25.4 kg.). A parallel to this and the strain imposed on his heart can be drawn. This may not be quite fair, but the end justifies the means.

Glands or Gluttony?

The decision whether obesity is due to an endocrine disturbance or to overeating is not in fact as important as it seems at first sight. With the exception of myxoedema all forms of obesity have to be treated by restriction of food and sometimes of salt and fluid intake. Glandular preparations administered by mouth or parenterally have, with the exception of thyroid, no effect on body weight. Thus the influence of castration in either sex, and of adrenal, pituitary, or hypothalamic disease, is not mitigated by extracts of these organs at present available. It is not implied that diagnosis is not important, but merely that in relation to obesity it helps us no further.

Myxoedema is not necessarily associated with gain in weight: in fact many myxoedematous subjects lose weight, probably because of poor appetite. It is certainly rare for obesity to be a presenting symptom. The hypothyroid woman complains rather of extreme lassitude, depression, irritability, loss of memory, and intolerable coldness. In any case the treatment is simple, though not devoid of dangers in the early stages. The more chronic the disease and the older the patient, the more important it is to give small doses of thyroid to start with. I have seen heart failure precipitated by the administration of 1 gr. (65 mg.) of thyroid a day for five days to a myxoedematous woman of 60. Withdrawal of the drug was fortunately followed by recovery from a critical state. Subsequently ¼-gr. (16-mg.) doses daily for a week, followed by twice this amount for three weeks, led to a steady recession of her hypothyroid signs. It was then possible to give 1 gr. twice a day with safety, and full recovery ensued.

Rarities seldom come singly. In the last year I have seen two examples of Rathke's pouch tumours involving the hypothalamus. In each case the leading symptom was obesity. Both were middle-aged patients and had been fat from childhood. They had large appetites, in one amounting to gluttony. In one headaches and restriction of the visual fields, in the other unsteadiness of gait, led eventually to the correct diagnosis. Both died in spite of surgery. These examples are intended as a warning that if persistent and increasing obesity should be associated with headache or change of behaviour every effort should be made to exclude a neurological cause, even though the patient may have been fat for years and possessed of a voracious appetite.

Common Causes of Obesity

In general it is safe to assert that if fat is increasing the body is receiving more food than it needs. Frank gluttony is not common nowadays, and as in any case the glutton will refuse our advice it would be pointless to waste time on him. Far and away the commonest age for obesity is from 40 years on.

What are the factors which lead to a disturbance of equilibrium between intake and output? They are: (1) Repeated childbirth, no doubt at times responsible for some resetting at a higher level of the central mechanism for maintenance of weight. Often the connexion is simply that the woman is more and more tied to the house by her children. She devotes herself

to feeding them, and is only too apt to join them at their large carbohydrate "teas" and then to keep her husband company at dinner. (2) Increasing security and more money to spend on large meals. (3) For the same reason, adding many calories to the daily food intake by consuming strong alcoholic drinks. (4) Increasing distaste for exercise. (5) Business luncheons, often vast and alcoholic.

This middle-aged obesity is quite simple to control. The following diet will restore the body to normal proportions:

Breakfast.—Two cups of tea or coffee. One slice of toast or bread, not more than 1 oz. (28 g.) in weight. Butter thinly spread. Boiled or poached egg or fish (boiled or steamed) or tongue. No sausages. Fresh fruit except banana.

Luncheon.—Clear meat soup if desired. Any green vegetables, celery, salsify, asparagus *ad lib.* No root vegetables, rice, or macaroni. Fish or lean meat, including fowl, *ad lib.* (no bread crumbs or bread sauce). Fresh fruit, except banana. Half an ounce (14 g.) of cheese. Bread and butter as for breakfast. Water or soda water.

Tea.—Two cups of tea. No food.

Dinner.—As for luncheon.

Saccharin may be used for sweetening. Milk may be taken in tea, but not more than half a pint (284 ml.) daily. One cocktail or one sherry *and* one glass of wine daily are permitted. Food must not be cooked in fat or oil. Worcester sauce, pepper, mustard, and vinegar are allowed. Salt to be used in cooking only.

Therapeutic Obesity

Overeating prescribed as a form of treatment often causes annoyance by virtue of ensuing obesity. I refer to the frequent meals advised to most sufferers from duodenal ulcer. The patients who keep to their instructions and drink milk between meals and at bedtime are horrified by a protuberant though now painless abdomen. The abandonment of tobacco smoking as a therapeutic measure or from caprice is well known to cause obesity because of the great increase of appetite. The peptic ulcer patient can be helped by substituting for milk a protective emulsion with no food value, such as:

Bism. carb.	gr. 40 (2.6 g.)
Mag. trisil.	gr. 20 (1.3 g.)
Mucil. acac.	q.s.
Tinct. aurant.	min. 10 (0.6 ml.)
Aq.	ad. ½ oz. (14.2 ml.)

This dose to be taken in place of milk or olive oil. The antacid effect is negligible, but so is that of milk. The bismuth forms a protective pellicle and can be seen on the surface of an ulcer long after the stomach has emptied itself.

Familial or Genetic Obesity

Under this heading we have most of the really difficult cases in which overeating does not seem to play a part—the hugely fat patient afflicted by excessive weight, often from early childhood. Here also we meet localized fatness—vast buttocks and lower extremities upholding a normal torso. Again in this class we meet corpulent patients whose body weight is in part maintained by excessive retention of fluid.

In all these cases it is wise to undertake treatment only if the patient is prepared to go to bed, preferably in hospital. The dietetic measures have to be severe, the fluid restriction being irksome and often intolerable to any patient who is ambulant and subjected to gastronomic temptation.

All these patients need a much stricter diet than that given above. Fat must be drastically reduced because of its high calorie value and because large stores are present in the patient's body. Carbohydrate is moderately reduced, though its exclusion is tolerable for a few days. Protein is the least affected, because the specific dynamic action of protein increases body metabolism. All this was quite simple in the days when food was plentiful, but the great shortage of protein foods makes scientific dieting very difficult. If the patient keeps chickens the protein is easy to get.

A pound (0.45 kg.) a day will be lost on the following diet:

Breakfast.—One egg and 1 oz. (28 g.) of bread or toast. Fruit juice.

Luncheon.—One egg or 1 oz. of corned beef and vegetables as below. Fruit juice.

Dinner.—Meat soups. Lean meat or fish, 4 oz. (113 g.), and vegetables as below. Fruit juice.

Food may not be fried. Water as much as needed (unless water retention is suspected).

Vegetables: Lettuce, cucumber, spinach, asparagus, endive, celery, mushrooms, tomatoes, sprouts, watercress, cauliflower, cabbage.

Once a week the patient may have one meal of any food he likes. This is encouraging and does no harm, because his capacity for large meals falls rapidly.

Vitamins A and D should be supplied as liq. vitamin A et D conc. (*B.P.*) 5 min. (0.3 ml.) daily.

After three to four weeks on this drastic diet enough weight will have been lost to allow the patient to pass to the following diet:

Breakfast.—Fresh fruit. Egg or fish. Coffee, tea. Bread, 2 oz. (57 g.).

Luncheon.—Lean meat, fish, or fowl, 3 oz. (85 g.). Green vegetables. Fresh fruit.

Tea.—Tea.

Dinner.—Meat, fish, or fowl, 3 oz. green vegetables.

9.30 p.m.—Half a cup of orange juice.

In addition one and a half glasses of skim-milk daily (for calcium content).

Vitamins as before.

When the desired weight is attained the diet should be slowly increased by adding butter, bread, and other vegetables. With a little care it is surprisingly easy to avoid a return to obesity.

Patients who retain water and salt are often pasty in appearance but rarely show pitting oedema. They pass but little urine when up and about, but notice increased output if kept in bed. More specific water-balance tests will show a greatly delayed output of a measured volume of fluid. If these patients do not lose weight on the above diets or if the loss is inadequate, salt should be forbidden and fluid intake limited to 1½ pints (850 ml.) daily. Inj. mersalyl. (*B.P.*), 1 ml., should be given intramuscularly twice weekly. The result of the above measures should be a copious diuresis and fall of weight. The treatment can be tolerated for two to three weeks. Thereafter salt may be used in cooking but not otherwise.

Starvation Treatment

Clearly the quickest way to ensure loss of weight is to deprive the patient of all food and allow water only. As a preliminary step, when dealing with the

more obstinate forms of obesity, this is justifiable for a few days and is suitable for young adults. Although after the first three days the craving for food rapidly diminishes, mental depression is profound. Few patients will tolerate such treatment for more than a week, and indeed prolongation of starvation beyond this point is inadvisable.

Less obvious starvation may be followed, though with reluctance, for two to three weeks. By this I mean a diet of fruit juices and lettuce only. It has a vogue among the wealthier classes, who seem to enjoy paying enormous fees for incarceration in clinics in order to be weaned from the delights of the table.

Exercise

There is no more disappointing scheme for the reduction of fat than that which depends on vigorous exercise. The fact is that a great amount of muscular work is needed to produce appreciable weight loss. An obese patient is seldom capable of carrying this out. In any case the appetite is increased and the essential food restriction is thus made more irksome.

The main value of exercises is to tone up muscles rendered flabby from sedentary habits and fatty overlay. They play a great part in restoring abdominal girth to normal proportions and, if persisted with, certainly help to prevent recurrence of belly fat when the strict regimen is at an end. No exercises are of value unless they can be practised often and inconspicuously throughout the day. Space will not allow a full description of these, but I refer to many of those outlined in Hornibrook's well-known book *Culture of the Abdomen*. They are incidentally an excellent corrective of constipation.

Drugs

The use of thyroid for myxoedema has already been discussed. In other obese states its administration may cause some loss of weight owing to a diuretic action and to slight elevation of the metabolic rate. In general the drug is disappointing, and unpleasant tachycardia may be induced by its use.

Dexamphetamine sulphate has a pronounced action in causing loss of weight. Its main effect is to reduce or abolish appetite. A dose of 5 mg. should be taken half an hour before breakfast and luncheon, and at 4 p.m. It should not be taken later, as it is apt to cause insomnia. The loss of weight is not entirely due to effect on appetite, because it is seen on a fixed calorie intake. The anti-obesity effect gradually wears off and will be negligible at the end of three months. It is not suitable for elderly people or for those with cardiovascular or cerebral diseases.

How many students are there in Britain, and what are they studying? A recent publication of the University Grants Committee, for the academic year 1948–9, shows a total of 83,690 full-time students: this figure includes 2,589 from foreign countries and a further 3,335 from the British Commonwealth. They are distributed among the various faculties as follows: medicine 16.8%, dentistry 3.1%, pure science 19.2%, technology 13%, arts 44.4%. Full-time teaching staff totalled 7,390. The total expenditure for the year was £18,022,094, the income being nearly 60% by Parliamentary grant, 20% from fees, 5% from local authority grants, 6.7% by endowments, and 1.9% from donations and subscriptions. It is interesting to compare the size of the Parliamentary grant in 1932–3 (£1,680,000) with that for the current year, 1950–1, which is £23,284,150, to appreciate the growth of university education and facilities.

SMALLPOX

On January 26 Professor A. W. Downie delivered a special University of London lecture at the London School of Hygiene and Tropical Medicine on "Infection and Immunity in Smallpox," a subject which the Brighton epidemic makes very topical.

In considering the pathogenesis of the disease it was not possible to speak dogmatically about many stages in its development. The disease was too severe to permit experiments with human volunteers, and, although recently Dr. Fenner had accumulated much exact information about mousepox, this laboratory model could at best only provide analogies. Therefore in discussing smallpox one must still be content to speak of probabilities.

Path of Infection

In man infection normally occurred through the respiratory tract, but whether or not there was a primary lesion was unknown. In mousepox the infection occurred through the skin and the primary lesion was visible. Manifest variola lesions in the upper respiratory tract and in the mouth were quite commonly seen in man during the stage of efflorescence, so that the failure to observe a primary lesion suggested that it was either very inconspicuous or situated in an inaccessible part of the respiratory tract. After infection there was an incubation period of 11–14 days before there were any signs of illness. If generalized disease occurred after variolation (inoculation with variola virus) the incubation period was often two to three days shorter than this, and the same was seen in infants infected congenitally.

What became of the virus during the incubation period was a matter for conjecture. From analogy with mousepox the virus probably found its way very rapidly to the local lymph nodes, where it multiplied: indeed, in variola the local lymph nodes might well be the primary focus, the mucous membrane of the respiratory tract merely allowing entry to the virus but not its multiplication. After multiplication in the regional lymph nodes there was probably a mild viraemia, with spread of the virus throughout the body. The virus was quickly removed from the blood stream by phagocytic cells and continued to multiply mainly in the liver, spleen, and bone marrow. Although the evidence was not conclusive, Professor Downie suggested that the lungs might also be a site of multiplication at this stage.

The incubation period terminated with a second viraemia, much more massive than the first. (In instances of congenital infection the baby became infected at the time of the mother's massive secondary viraemia). At this point the clinical illness might be said to begin, though the skin rash did not appear for another one or two days. During the whole of the incubation period and up to the time of the appearance of the rash, there was good evidence that the patient was not infective. Where contacts had been allowed freedom of movement no secondary cases had resulted from such contacts incubating the disease. If smallpox were, like influenza, highly infectious from the onset of illness control of outbreaks by our present policy of isolation of cases and vaccination of contacts would be very difficult.

The Immune Response

After the appearance of the skin rash the course of the disease was dominated by the immunity response and the development of antibodies. These could be measured in three ways: by a neutralization technique using the method of inoculation on the chorio-allantoic membrane of chick embryos, by a haemagglutinin-inhibition test, and by the less sensitive complement-fixation technique.

After vaccination antibodies could first be demonstrated in 10–12 days, and they reached their peak in 20 days. Thereafter their demonstration depended upon which test was used for their detection. By the neutralization test, antibodies might be detectable for 40 years or more, though

individual differences occurred. Such differences might in part account for the occurrence of variola in patients previously successfully vaccinated. By the haemagglutinin-inhibition test, antibodies after vaccination could also be demonstrated up to one to two years, though their titre usually declined. In contrast complement-fixing antibodies fell very rapidly, the test being usually negative a year after vaccination.

In variola, antibody could usually be detected 4–5 days after the start of the clinical illness. Although antibodies probably began to appear a day or two before they were measurable, it seemed certain that the antibody rise which followed infection occurred later than the rise following vaccination, and this was why vaccination during the first few days of the incubation period was able in many cases to abort an attack of variola: if there were sufficient circulating antibodies at the time of the secondary viraemia no skin rash would appear. Once the rash had developed, the subsequent rise of antibody did not affect the course of the skin lesions, because these were the result of injury to cells before the antibodies had had time to quell the infection. In those patients who would recover, the viraemia was usually difficult to demonstrate and then only on the first day of the clinical illness, for it was quickly suppressed by the vigorous immune response. Conversely, those patients who had low antibody titres during the first week were often those who clinically were toxaemic. It was only in those patients who failed to have a satisfactory antibody response that the viraemia persisted and death ensued.

As after vaccination, complement-fixing antibodies commonly disappeared within a year of recovery from infection, but haemagglutinin-inhibiting antibodies and neutralizing antibodies persisted for long periods.

To many in the audience these facts about the immune response to the variola and vaccinia viruses must have proved the most interesting part of a fascinating lecture, and it is fitting that this should have been so, since Professor Downie has himself contributed so much to our knowledge of these aspects of the disease.

MEDICAL FOUNDATION OF EPSOM COLLEGE

The Royal Medical Foundation of Epsom College appeals to all members of the medical profession who do not already do so to subscribe to the Foundation, the object of which is to help the families of less fortunate colleagues. The Foundation in 1950 has provided nearly £20,000, as follows:

	£
50 ordinary pensions to medical men or their widows	1,500
47 Foundation scholarships for boys (educated, clothed, and maintained entirely free of cost)	10,790
15 scholarships for girls	429
Education of 25 boys at reduced fees	1,472
140 pensions and annuities of varying amounts ..	3,020
Grants towards education of 64 boys and girls ..	2,326
Grants to medical men, widows, and spinsters ..	260

In order to maintain this assistance the Foundation has to rely upon the generosity of subscribers and donors for over £16,500 a year. Without sufficient help from them the existing benefactions would have to be curtailed. The Sherman Bigg Fund enables the Foundation to make educational grants for those who cannot obtain scholarships. Donations to augment the income of this Fund will be most welcome. Subscriptions and donations for whatever aspect of the work may be sent to the secretary, Epsom College, Surrey.

The I.C.I. film catalogue gives details of all the films of medical, agricultural, and general interest available on loan without charge from the I.C.I. Film Library, Bolton House, Curzon Street, London, W.1, which will also supply free copies of the catalogue on request.

Reports of Societies

THROMBOPHLEBITIS

On January 23 the Section of Medicine of the Royal Society of Medicine discussed "Thrombophlebitis." Dr. C. E. LAKIN, president of the Section, was in the chair.

Professor W. MELVILLE ARNOTT (Birmingham) opened the discussion by saying that it was his task to indicate the major problems, to summarize the relevant knowledge, and to outline the gaps in such knowledge. Thrombophlebitis was characteristically a complication of injury, using that term in its widest sense. But, then, what was the exact relationship between thrombophlebitis and such predisposing conditions as myocardial infarction or a gastrectomy operation? Professor Arnott reviewed the role of local trauma, thrombocytosis, endothelial changes, and disturbances of the venous circulation, as well as the effects of malignant disease, age, obesity, and venous varicosities, in the aetiology of the condition. While many surgeons were fully alive to the early diagnostic features, he feared that physicians seldom made a routine search for evidence of thrombosis. He stressed the importance of training house-physicians to examine the legs of medical patients, for so often chest complications were due to pulmonary embolism. He also underlined the dangers of deep-breathing exercises in patients who had symptoms suggestive of embolism.

Anticoagulant Therapy

In assessing the results of treatment Professor Arnott said that many of the published figures were worthless owing to neglect of the most elementary statistical principles. Not being the possessor of an adequate personal series, he intended to base his views on the reports of those who seemed to have some appreciation of the scientific method. He then referred to the conclusions drawn by Cosgriff* from a collected series treated both with and without anticoagulants. Cases given so-called conservative treatment (i.e., neither anticoagulant treatment nor vein ligation) could safely be regarded as a "no treatment" control series. The vastly superior results attained with anticoagulant drugs left little doubt about their efficacy, and he roundly condemned the withholding of such treatment if reliable laboratory facilities were available.

He then discussed some of the problems of heparin therapy: he mentioned the control of dosage, the use of "retard" preparations, and the time for which treatment should be continued. He believed that treatment should usually be given for at least two weeks. One of the chief problems affecting treatment with dicoumarol drugs was the setting up of a reliable laboratory service. On the one hand there was the danger of overdosage, on the other the risk that the clinician would be lulled into a sense of false security by the low prothrombin levels. It was his impression that much of the opposition to anticoagulant therapy was due to a failure to realize that its successful use demanded clinical and laboratory care comparable to that required in a severe case of diabetes.

Professor Arnott concluded by saying that there was no incontestable proof that early movements and ambulation significantly lowered the incidence of thrombosis.

Physiological Background

Professor K. J. FRANKLIN (London) said that, as a physiologist interested in the venous system, he had been invited to provide the necessary background for the clinical study of the disorder. His earlier interest and recent discussion with several colleagues had made him feel exactly the opposite

*Amer. J. Med., 1947, 3, 740, 753.

of someone who, having attended a philosophical lecture at Oxford, made the comment, "Nothing emerges, but the concept strengthens."

Despite the title of the discussion Professor Franklin felt that it would embrace phlebothrombosis as well as thrombophlebitis, and he showed how difficult it was to separate these two entities. No part of the circulation should be considered in isolation from the rest, but he would confine himself mainly to conditions in the lower limbs, since from the clinical point of view this was the most important site of thrombosis. In haemorrhage and shock the skin and non-essential skeletal musculature were the first to suffer in the redistribution of blood, and the lower limbs when they were inactive suffered most of all. Here then was a local factor of some importance. After describing various degenerative changes in the valves and walls of the veins, Professor Franklin then referred to the possible production of "vaso-excitor material" (V.E.M.) and "vaso-depressor material" (V.D.M.) in the anoxic renal cortex and liver, respectively, as a result of impaired circulation. Any vasotropic factors of this kind would further depress the tissue circulation in the inactive lower limbs. Added to this was the possibility of deep venous spasm. Payling Wright's studies had shown that, although there was post-operative slowing of the venous return from the legs of those confined to bed, this did not happen in ambulant patients. Some *local* change must be responsible for the local predilection to thrombosis, and, even if primary histological changes were not evident, there was a possibility of functional changes in the wall of the vein. Slowing of the venous flow increased the opportunity for thrombogenic factors to take effect, and the rationale of such therapeutic factors as exercise, paravertebral block, and even in part of heparin might lie in their antispasmodic effect.

In discussing the role of the platelets Professor Franklin differentiated between the true thrombus and the clot which was formed in phlebothrombosis, and he then summarized some current views on the coagulation of the blood. He referred to the thermostable and thermolabile components of the prothrombin complex and said that the former (compound A) could exist in active and inactive forms. Dicoumarol and avitaminosis K reduced the amount of the thermostable fraction only. The platelets were not the source of thromboplastin but they liberated an enzyme which activated the thromboplastinogen in the plasma. However, this more complex conception of blood coagulation had not as yet contributed to their understanding of the aetiology of thrombophlebitis. He concluded by saying that the localizing influences in thrombosis should be sought in the vein wall or the tissues drained by the vein. Various precautionary measures suggested themselves to a physiologist: first, the avoidance of anoxaemia and tissue anoxia; secondly, the avoidance of factors (including psychological ones) causing overactivity of the sympathetic nervous system; and thirdly, the use of any measures which would exercise the leg vessels.

Ilio-femoral Thrombosis and Deep Phlebitis of the Calf

Professor A. M. BOYD (Manchester) said that he and his colleagues had investigated the late effects of thrombophlebitis in 262 patients. He believed that they could be divided into two main groups, depending on whether the thrombosis started distal or proximal to the valve in the popliteal vein which was situated immediately below the entrance of the small saphenous vein. Those starting above this valve he regarded as examples of ilio-femoral thrombosis, and those below it were examples of deep phlebitis of the calf. He believed that the classical ilio-femoral thrombosis extended from the adductor opening to the point where the internal iliac artery crossed and tended to obstruct the external iliac vein. More often, however, the thrombotic process stopped just below the junction of the deep and superficial femoral veins, and rarely it extended up into the vena cava. Deep phlebitis of the calf usually originated in the muscular tributaries from the gastrocnemius and soleus muscles. He thought that the popliteal vein was in a vulnerable position at the upper border of the femoral condyles where it was attached to the oblique ligament of the knee-joint and could be damaged by flexion and extension strains.

Professor Boyd went on to say that ilio-femoral thrombosis was usually seen in puerperal women of over 30 who commonly had varicose veins. The non-puerperal cases were post-operative, post-pneumonic, traumatic, or spontaneous in origin, the last-named often suggesting some occult malignant disease. He divided his cases into acute, subacute, and chronic types. Ilio-femoral thrombosis was usually acute, whereas deep phlebitis of the calf was most often subacute or chronic. The pain in acute cases was variable and depended on the degree of arterial and venous spasm. He then detailed the clinical features of the two main groups of cases and said that pain was a striking feature of the ilio-femoral group. When severe pain occurred in calf-vein thrombosis it was probably due to involvement of tributaries around the posterior tibial nerve. Subacute phlebitis of the calf was usually due to injury; chronic phlebitis was usually a sequel to the acute phase, but occasionally it was a primary condition in the calf.

Turning to the question of management, he said that neglected deep thrombophlebitis led to varying degrees of disability. The patient with a previously normal circulation might suffer little, but in what he termed the "erythrocyanoid" patient the blood vessels were hypoplastic and there were likely to be more serious effects from a thrombosis. He believed that even in the most enlightened circles it was unusual for cases of acute thrombophlebitis to be treated before the third or fourth day. The condition was an acute emergency, and he recommended immediate paravertebral block with 20 ml. of 1% procaine and elevation of the lower limbs. The patient should get up on the fourth day or as soon as the pulse and temperature had settled. All cases should be provided with effective compression bandages or elastic stockings.

In cases of chronic thrombophlebitis (i.e., venous insufficiency due to old thrombosis) it was essential to investigate the case fully and to decide if the changes were reversible or not. It was their practice in Manchester to do ascending and descending (retrograde) phlebograms as well as to measure the venous pressure during exercise. The arterial circulation, too, must be carefully assessed to exclude any contributory insufficiency. Efficient support of the leg was essential, and he believed that vitamin E in large doses might perhaps be of value. Operative treatment of some sort had been undertaken in 122 of their 262 cases, and this had included sympathectomy, ligation of the superficial femoral vein, or ligation of the popliteal vein. While their figures did not permit any final conclusions he believed that sympathectomy was the most valuable of the operative measures.

General Discussion

After the opening papers the discussion was continued by a number of other speakers. Mr. B. N. CATCHPOLE (Manchester) briefly described the method of measuring venous pressure used in the examination of Professor Boyd's cases, and Mr. S. ROSE (Manchester) gave an account of their phlebographic technique. Dr. S. M. RIVLIN (London) said he was surprised that nobody had bothered to mention superficial thrombophlebitis. This was a common complaint and could extend into the deep veins. It was best treated by applying adhesive strapping to the limb. He knew that Professor Boyd had the strongest objections to the retrograde injection of varicose veins, but he himself did not think the practice harmful. It probably depended on how much was injected and the way in which it was done. Mr. SOL COHEN (Gravesend) said that the discussion so far had not given any real guidance on the treatment of thrombosis. He would like to suggest what he believed to be a rational method. First, early cases with minimal signs should be treated by paravertebral block. Secondly, those with oedema and more extensive signs should be

treated with anticoagulants. Lastly, in those cases in which embolism had already occurred the femoral veins should be tied.

Mr. HUGH MCLAREN (Birmingham) said that Professor Boyd seemed to have been talking of a totally different disease from that which he saw in a gynaecological unit. He emphasized that the nursing staff must be trained to detect the earliest signs and thus enable a really early diagnosis to be made. This had been their practice and they had been able to treat their cases with anticoagulants at the earliest possible stage. Mr. S. LEE (London) referred to the work of Ochsner, who had suggested that the antithrombin content of the plasma could be increased by the administration of vitamin E. He himself was trying vitamin E and hoped to be able to publish some results before long. Mr. W. MCKIM MCCULLAGH (London) said he firmly believed that infection was a most important cause of thrombosis and embolism. In practically all of his cases there had been some rise of temperature, which he thought was good evidence of sepsis. Professor BOYD, in reply, having dealt with several points raised by other speakers, said that he did not use the anticoagulants. He thought that many so-called pulmonary emboli were really examples of pulmonary thrombosis. If arterial thrombosis occurred in the limbs why should it not also occur in the lungs?

OSTEOARTHRITIS OF THE HIP

At a meeting of the Section of Surgery of the Manchester Medical Society on January 9 Mr. JOHN CHARNLEY opened a discussion on "Osteoarthritis of the Hip." He said that the future of the surgical treatment of the osteoarthritic hip depended on the possibility of constructing a new hip-joint. The fundamental difficulty was that in osteoarthritis stability after operation was rarely compatible with mobility, and it seemed doubtful whether any detail of technique would prove this principle to be false. Many operations on the hip-joint necessitated elderly patients being separated from their homes and confined to hospital from five to six months, and even then there might be only trivial improvement. Surgery had nothing to offer the mild case of osteoarthritis of the hip.

Elderly patients could not tolerate an arthrodesis because they were less agile than young patients; but an arthrodesis carried out in the first half of life was easily accommodated by the lumbar spine and would last 30 years of full activity. On the other hand an arthroplasty performed in the first half of life would probably not last more than 10 years, and it rarely increased the range of movement.

A New Operation

Intertrochanteric osteotomy as developed by McMurray had the advantage that as the hip still preserved a small range of movement the lumbar spine in elderly patients was not exposed to the same strain as after arthrodesis. But owing to the prolonged wearing of a long hip spica, and the resulting stiff knee, the patient usually did not feel benefit from the operation for about 12 months; indeed, at six months the patient might be very considerably more disabled than before his operation.

Many workers were trying to combine the benefits of the osteotomy principle with internal fixation, so as to preserve the mobility of the knee. Mr. Charnley then described his own method of doing this. In his operation the hip was converted into a central dislocation by reducing the side of the femoral head and boring a hole through the floor of the acetabulum; the head then sank into the pelvis until the trochanters impinged against the side wall of the pelvis and so blocked adduction. As all rotation was immediately prevented, only a short hip spica was required, and early knee movement could thus be obtained. The plaster could be discarded as early as four weeks after the operation, and the patient could then take weight on to the neck of the femur. These cases achieved a range of 20 to 30 degrees of movement in the hips in the flexion–extension plane. They were able to go home six weeks after operation, and therafter required no physiotherapy. They felt better for the operation within three months and an end-result was achieved in six months.

Surgery or No Surgery

Mr. D. LL. GRIFFITHS said that it was becoming increasingly apparent that primary degenerative arthritis of the hip was not a condition for which surgical treatment could often afford lasting relief. The best results of any form of surgery were to be obtained in unilateral degenerative disease which was secondary to injury or to a congenital abnormality. As a broad generalization, the "good case" for any one specific operation was an equally good case for an alternative surgical procedure. It was more a decision between surgery or no surgery than between arthrodesis or arthroplasty.

Operations upon the nerve supply of the hip had proved thoroughly disappointing. There was probably no surgical short cut to painlessness in osteoarthritis. Subtrochanteric osteotomy, though of great value in correcting deformity, gave disappointing results in the long run. Arthrodesis was excellent for strictly unilateral disease which would certainly remain unilateral, but bony fusion was not easy to obtain and the operation was of limited value in elderly people.

Of reconstructive procedures, excision of the head and neck of the femur with or without a plated osteotomy was, in the speaker's experience, of very limited value. The best results from any operation were those obtained from arthroplasty of the Smith-Petersen type using a vitallium mould. This operation was a complete reconstruction of the hip joint. The vitallium "cup" was not to be looked upon simply as an interposition structure, but as a mobile element which led to re-formation of articular surfaces on each side of it.

The recent introduction by the brothers Judet of an operation in which the head of the femur was replaced by an acrylic prosthesis was still very much under trial in this country. The immediate results were very promising, and if the operation stood the test of time it might become the best procedure, if only because of its simplicity and the easy after-treatment.

FOETAL ASPHYXIA

At a joint meeting of the Sections of Pathology and Medicine of the Manchester Medical Society, held on January 10, Dr. A. R. MACGREGOR read a paper on "The Role of Asphyxia in Foetal and Neonatal Mortality." Pathological changes indicating asphyxia were found more often than any other condition at necropsy in cases of foetal and early neonatal death, but their importance was not always appreciated. They had been present in 64 out of 100 consecutive stillbirths and in 46 out of 100 consecutive neonatal deaths; and although in a number of these cases death could be ascribed to another cause, such as haemorrhage or pneumonia, in many of them asphyxia was the primary condition.

It was known that from an early stage of gestation the foetus could make respiratory movements. These were ordinarily rapid and shallow, but asphyxia caused them to become deep and gasping. It was disputed whether these movements occurred under perfectly normal conditions, and whether they resulted in liquor amnii being inhaled into the lungs. Some of the best observers had concluded that the foetus was normally apnoeic, and that inhalation of liquor amnii was not a physiological occurrence.

Liquor amnii in the lungs was readily recognized microscopically. Such inhaled material might prevent the establishment of breathing at birth, but in many cases death was due to central respiratory and cardiac failure. Asphyxia was also an important cause of certain other lethal conditions,

such as atelectasis, most types of foetal and neonatal haemorrhage, and pneumonias occurring before or soon after birth.

A study of the relation of asphyxia to prematurity showed that many stillbirths of both mature and premature foetuses were due to asphyxia, but that, among the live-born, deaths due to asphyxia occurred usually in premature infants. The chance of survival of asphyxiated live-born mature infants was good, if infection could be prevented; but the risk for the premature infant was much greater. The usual causes of foetal asphyxia were interference with the circulation of blood through the placenta and cord, and maternal anoxaemia. Some observers thought anaesthesia to be the most frequent single cause of foetal asphyxia.

CHEMOTHERAPY IN TUBERCULOSIS

A meeting of the Liverpool Medical Institution was held on January 11 with the president, Dr. DAVID JOHNSTON, in the chair. Three papers were read on "Chemotherapy in Tuberculosis."

Summary of the Present Position

Dr. O. F. THOMAS said that the value of *para*-aminosalicylic acid (P.A.S.), first reported by Lehman, had been confirmed; it quickly improved the general condition and relieved symptoms without, however, producing much radiological change. Unfortunately, unpleasant side-effects, particularly nausea, were produced with effective dosage. Streptomycin used in the right type of lesion had produced good results even in advanced cases. With the present-day dosage of 1 g. toxic reactions had not been found troublesome, but the late results in meningitis had not been as favourable as was at first hoped. The disturbing factor in the use of streptomycin had been the emergence of resistant strains, to the extent of 70% of cases by the fourth month of treatment.

Combined therapy with streptomycin and P.A.S. (*Journal*, November 11, 1950, p. 1073) was superior to treatment with either substance alone. Clinically the patients in the combined group fared better in every way, and only 9% developed resistant strains. More recent work indicated that low losage of P.A.S. did not prevent the development of resistance: when given with streptomycin a daily dosage of 20 g. of P.A.S. should be administered.

The thiosemicarbazones had been used extensively on the Continent. Good results had been claimed, but in high dosage they were toxic products. These drugs were about to be compared with P.A.S. in a controlled trial, from the point of view of the clinical response and their ability to prevent resistance when given in a safe dosage.

In pulmonary tuberculosis all these chemotherapeutic substances were indicated in recent exudative disease, acute spreads, and in laryngeal and endobronchial disease. They rendered more patients suitable for well-established treatments such as collapse therapy and surgery.

Dr. R. McL. TODD referred to the first cases of tuberculous meningitis, miliary tuberculosis, and tuberculous bronchopneumonia which had been treated in Liverpool with streptomycin (*Journal*, April 17, 1948, p. 747). Streptomycin had prolonged the lives of these patients, but the early hopes of "cure" had not been realized, because of recurrences of meningitis several months after apparent recovery. Many factors, in addition to streptomycin, contribute to the successful treatment of patients with tuberculous meningitis—the age of the patient, the duration of the illness before the start of therapy, the presence of other tuberculous lesions, the resistance of the tubercle bacillus, and the quality of the medical and nursing supervision. Attempts to achieve a more satisfactory response to therapy had proceeded along three main lines:

(1) The regime of therapy had been varied, particularly the duration and rhythm of treatment and the route by which intrathecal streptomycin was given. Short courses of intrathecal streptomycin were more efficacious than prolonged courses. Except in those patients with marked papilloedema when first seen, the introduction of streptomycin into the lateral ventricles did not affect the prognosis. (2) Other drugs, particularly P.A.S., had been given both orally and intrathecally in addition to streptomycin, and this had led to an improvement in the long-term results. (3) Attempts had been made to prevent fibrin formation by using heparin or streptokinase, but without much apparent success; but definite improvement had taken place after intrathecal injections of tuberculin (P.P.D.).

During the three-year period from January, 1947, 51 children with tuberculous meningitis had been treated; in 10 of these (20%) the cerebrospinal fluid had been normal for at least 12 months, and physically and mentally these children appeared well. Of 20 children with tuberculous meningitis and miliary tuberculosis three (15%) were normal in every respect after a similar period.

Trial of P.A.S. in Primary Tuberculosis

In view of these disappointing long-term results, an attempt had been made to assess whether the administration of P.A.S. in primary tuberculosis was of value in preventing tuberculous meningitis. P.A.S. in doses of 10 to 25 g. each day (sufficient to achieve a blood level of 8.5 μg. two hours after ingestion) was given orally in divided doses two-hourly to alternate patients in the same age group and, so far as could be ascertained, at the same stage of development of the primary complex. The comparison of the "treated" and "untreated" groups was made by observing the behaviour and clinical progress of the child, by determining the weekly weight gain, by serial sedimentation rates, and by the radiological changes in the lungs. The results of the pilot survey had been most encouraging, and indicated that P.A.S. was probably of value in the treatment of primary tuberculosis. During 1951 a full-scale controlled trial of P.A.S. in primary tuberculosis was being undertaken in Liverpool.

Caseous Lesions and Streptomycin Resistance

Dr. C. A. ST. HILL pointed out that, although the results of streptomycin therapy of tuberculosis had been encouraging in many forms of the disease, this drug had not been so outstandingly successful against tuberculosis as had penicillin in the treatment of staphylococcal infections. One of the supposed reasons for this was the suggestion that streptomycin could not penetrate into the depths of caseous tuberculous lesions. In order to test this hypothesis he had estimated the streptomycin content of a number of large caseous kidney lesions from patients receiving streptomycin treatment. All had shown concentrations of streptomycin varying from 2 to 8 units per ml. Tubercle bacilli had also been obtained from many of these lesions, and in every case they had proved resistant to the concentrations of streptomycin present in the lesions. It was suggested that caseous material promoted the acquisition of resistance by tubercle bacilli.

Another possible reason for the relative failure of streptomycin might be that the tubercle bacillus was not very sensitive to the drug even at the best of times. Detergents appeared to increase the sensitivity of tubercle bacilli to streptomycin *in vitro*.

After the papers there was a general discussion, to which Drs. V. COTTON CORNWALL, A. C. KIRBY, R. E. REWELL, and J. K. B. WADDINGTON contributed.

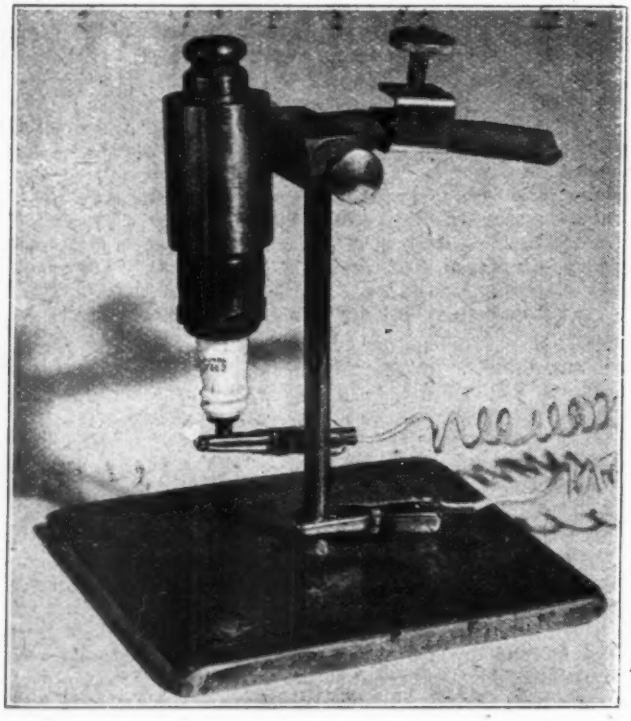
The following items have recently become available: (1) *Checklist of U.S.A. and Canadian Library Holdings of Austrian, Belgian, French, and Italian Medical and Dental Periodicals, 1939–48.* Copies ($2) may be obtained from Mr. F. G. Kilgour, Medical Library Association, 333, Cedar Street, New Haven 11, Conn., U.S.A. (2) *Selective List of Latin-American [Medical] Serials.* Copies may be obtained gratis on request to Mr. J. Groesbeck, Acquisition Division, Army Medical Library, Washington 25, D.C., U.S.A.

Preparations and Appliances

APPARATUS FOR DEMONSTRATING THE EXPLOSIVE PROPERTIES OF ANAESTHETIC GASES AND VAPOURS

Dr. H. J. V. MORTON, senior anaesthetist, Hillingdon Hospital, Uxbridge, writes: Most doctors know which anaesthetic gas and vapour mixtures are inflammable or explosive. Few know from actual experience how very explosive some of these mixtures really are. The simple apparatus illustrated here will demonstrate the explosive properties of gases in a safe but spectacular fashion. It may appeal not only to teachers of anaesthesia but also to anaesthetists unable by mere argument to convince their surgical colleagues of the undesirability of taking risks with cautery or diathermy.

The apparatus consists of a 2-in. (5-cm.) length of 1-in. (2.5-cm.) diameter steel rod drilled through and tapped at one end to take a motor-car sparking plug and turned at the other to hold a toy balloon (see illustration). It is



fixed to a convenient stand by a side tube through which the balloon can be filled with the mixture to be tested. A flash-lamp battery will cause a 6-volt car induction coil to make the necessary spark. A few yards of twin flex and a press-button complete the outfit.

Twenty per cent. cyclopropane in oxygen, or the mixture obtained by passing nitrous oxide (80%) and oxygen (20%) over ether in a Boyle machine, is suitable for demonstration purposes. It is unwise to explode more than a litre of such mixtures in a lecture-room. Experiments with larger quantities, and indeed the initial testing of any mixture, should be conducted out of doors in an open space and well away from hospital wards.

There are believed to be 15,000–20,000 cases of leprosy in Ethiopia, and W.H.O. is sending an expert to demonstrate the most modern treatments.

Correspondence

What Homoeopathy Is

SIR,—Some observations made about the middle of last century by Oliver Wendell Holmes may still be the answer to Dr. R. E. W. Oliver's questi n, "What is homoeopathy?" (January 27, p. 192). Holmes writes (*Currents and Countercurrents in Medical Science, with other Addresses and Essays*, Boston, 1861) of the homoeopathic materia medica as "sugar of milk and a nomenclature," and states that its pretensions and assertions cannot stand before a single hour of calm investigation. Its founder, Samuel Hahnemann, a German physician who lived in Paris and died in 1843, was never able to substantiate his doctrine of *similia similibus curantur* and the use of infinitesimal doses (e.g., $\frac{1}{100}$ of $\frac{1}{1,000,000}^{6}$ of a grain of oyster shell), while some ideas of his views on pathology may be gathered from the fact that he stated that seven-eighths of all chronic disease—for example, rickets, epilepsy, cancer, cataract, to mention only a few—were due to "psora," or the itch. Holmes remarks that it is sometimes said of homoeopathy, "At any rate it can do no harm. This may or may not be true as regards the individual, but it always does very great harm to the community to encourage ignorance, error, or deception in a profession which deals with the life and health of our fellow-creatures." His conclusion of the whole matter is that "it may be practised by shrewd men and by honest ones; rarely, it must be feared, by those who are both shrewd and honest. As a psychological experiment on the weakness of cultivated minds, it is the best trick of the century." Perhaps it is an equally good trick in this century also!—I am, etc.,

Cardiff. LAMBERT ROGERS.

SIR,—I would reply to the letter "What is Homoeopathy?" (January 27, p. 192) that homoeopathy is the product of an often-repeated observation, first clarified and fully investigated by Hahnemann in Napoleonic days. The observation was that a drug which will produce a certain disease picture in normal persons will tend to cure a diseased person presenting this picture if given in appropriate dosage. This, and this only, is homoeopathy. In the development of homoeopathy, industrious and sincere medical men have "proved"—that is, studied—the disorders produced in normal humans by hundreds of drugs, paying particular attention to the earliest manifestations, mainly symptoms. These studies have produced an immense literature, mastery of which is most difficult. An observation which has emerged in the course of the years is that the drug, if correctly selected, will produce its effect in incredible dilution. These observations, both so unlikely on the face of it, are the source of intense theoretical opposition, accusations of mumbo-jumbo, and so forth from those who have no practical experience. Those who have practical experience devote their intellect to the more practical task of mastering the pharmacopoeia, knowing that homoeopathy has much to offer those who succeed. Reinforcements are urgently needed to further the study of homoeopathy, particularly with a view to delineating the sphere of optimum influence of this form of therapy, and to producing reliable statistical reviews of the therapeutic efficacy of the system.—I am, etc.,

Bretby Hall, near Burton-on-Trent. R. LUNT.

SIR,—One would hesitate to ask you to open your correspondence columns to a full statement of the case for homoeopathy, and indeed one is surprised that it should even be necessary. However, if your correspondent (January 27, p. 192) is interested, then we would invite him to direct his inquiries to the Faculty of Homoeopathy, incorporated by Act of Parliament, which is registered at the Royal London Homoeopathic Hospital, Great Ormond Street,

London, W.C.1, and which holds regular meetings to which all medical men and women are invited. The Faculty supervises education courses for the study of homoeopathy, and awards certificates and diplomas after examination to fully qualified and registered medical practitioners. The Royal London Homoeopathic Hospital is a general hospital of 200 beds within the National Health Service and is, of course, staffed by fully qualified physicians and surgeons.—We are, etc.,

MARGERY G. BLACKIE.
P. G. QUINTON.

Faculty of Homoeopathy, London, W.C.1.

SIR,—Homoeopathy is a true science, based on systematic experimental observation.

Despite the great advances in all branches of medicine since it was first introduced, homoeopathy still has a place in therapeutics, especially in cases for which there is no definite orthodox treatment. The late Dr. C. E. Wheeler's book *The Case for Homoeopathy* answers Dr. Oliver's inquiry more fully.—I am, etc.,

N. J. PRATT.

Norwich.

Appendicitis at Sea

SIR,—One point which has not cropped up during this correspondence (January 20, p. 136; February 3, p. 245) is the influence of climate on the course of a case. It was, I think, fairly generally understood that in the region of the Arctic Circle one could take liberties which would perhaps be fatal in the Indian Ocean. Thus during a year on Northern patrol during the war we successfully "cooked" seven cases of appendicitis. One case went on to abscess formation.

But of course the number of operations done in ships varied greatly with the qualifications of the medical officers. I well remember my captain sending for me after he had dined with the captain of another ship employed on similar duties in the same latitude. The following conversation took place: "P.M.O., the *Blankshire* is getting ahead of us—they did over 50 major surgical operations during the last half-year! How many did we do?" "Nine, Sir. But then the S.M.O. of the *Blankshire* is an F.R.C.S."—I am, etc.,

FRANCIS W. BESLEY,
Surgeon Commander, R.N., retired.

Halesworth.

"Aureomycin" for Influenzal Pneumonia

SIR,—There has recently been an influenza epidemic in Liverpool. A notable feature has been the number of elderly people dying of associated pneumonias. A number of these have been resistant to sulphonamides and penicillin. It is impossible to get these people into hospital for aureomycin therapy, and I understand the Ministry of Health do not permit its use outside hospital. How, then, can I obtain treatment for my elderly patients in their own homes?—I am, etc.,

H. M. BLAQUIERE.

Liverpool.

Oral Penicillin and Gastric Acidity

SIR,—With regard to the letter from Dr. F. Bicknell (January 27, p. 191) and the paper by Dr. S. A. Doxiadis and his colleagues (January 6, p. 16), it seems there is still too much attention paid to the hope that most of the difficulties connected with oral penicillin therapy can be resolved by simply giving this drug with an antacid. Unfortunately, the neutralization of the acid in the stomach does not materially improve the absorption of the drug, at least in adults. That this observation is true was confirmed as long ago as 1946 by W. McDermott *et al.* (*J. clin. Invest.*, 1946, **25**, 190), who showed that no better absorption was obtained with penicillin by mouth in patients with achlorhydria.

H. C. Stewart and J. R. May (*Lancet*, 1947, **2**, 857) re-examined this problem, and showed that the acid of the stomach was not an important factor in the destruction of penicillin unless the acidity of the gastric contents was more acid than *p*H 3, which occurred only in a limited number of cases examined. Further, even in the very acid stomachs, it was only a small factor because the peak blood levels by mouth on an empty stomach are reached about 40 minutes to one hour after taking the drug, during which time little destruction takes place at this *p*H. It was concluded, therefore, that the alkali might help more by enabling the penicillin to leave the stomach more rapidly, as alkaline solutions themselves do, than by neutralizing the acid present. The best results were obtained by giving penicillin in about 4 oz. (114 ml.) of water, to which, if preferred, a soluble alkali could be added. The dose schedule should be four-hourly on as empty a stomach as possible, and if necessary glucose can be given at the same time as the penicillin. By duodenal intubation it was shown that penicillin appeared to be absorbed from the upper part of the duodenum over a relatively small area, and if the bulk of fluid was increased so that it would pass this area more rapidly the absorption of penicillin was much less.

With regard to Dr. Bicknell's suggestion that blood penicillin levels after oral doses should be investigated during illness and not during the irrelevant condition of health, from experiments I have done on numerous patients there would appear to be no difference in this respect, and therefore volunteers who act as normal subjects in these experiments can provide evidence which is useful and valid.—I am, etc.,

H. C. STEWART.

London, W.2.

SIR,—I should like to applaud Dr. Franklin Bicknell's plea (January 27, p. 191) for further clinical trial and investigation of oral penicillin in ill persons. Of the numerous reports of the efficacy of oral penicillin in bacterial infections there are two at least in which the lowered gastric acidity during illness has received recognition. Buchanan[1] and Anderson and Landsman[2] attributed some of their success with oral penicillin in children and adults respectively to the lowered gastric acidity during severe bodily infection. To this may be added the fact that penicillin is rapidly absorbed before any appreciable destruction by peptic acid can take place (Stewart and May[3]).

However, large doses are necessary, and I have found 600,000 units (unbuffered), 6–8 hourly, to be the minimum adult dose required for the treatment of acute conditions, such as tonsillitis, bronchitis, otitis media, etc., in general practice.

In the treatment of localized pyogenic infections (carbuncles, boils, etc.) I have not achieved much success with this oral dosage scheme, as compared with 24-hourly injections of crystalline penicillin.[4]

The enormous saving of time resulting from the use of the oral route in general practice justifies the expense of the method. With more extensive use the price will doubtless fall, just as the present-day price of penicillin per injection has resulted from its copious use.—I am, etc.,

DAVID WHEATLEY.

Twickenham.

REFERENCES

1 Buchanan, J. L. (1946). *Lancet*, **2**, 560.
2 Anderson, T., and Landsman, J. B. (1947). *British Medical Journal*, **2**, 950.
3 Stewart, H. C., and May, J. R. (1947). *Lancet*, **2**, 857.
4 Wheatley, D. (1949). *Practitioner*, **162**, 508.

Sensitivity to Procaine Penicillin

SIR,—The suspension preparation of the procaine salt of crystalline penicillin has now been in use for a considerable time and has proved a most valuable therapeutic agent. Untoward reactions from its use seem to be so rare that it is thought the following case of idiosyncrasy to the preparation may be worth recording.

A chronic bronchitic man, aged 48, of plethoric build, was admitted recently with a temperature of 101.2° F. (38.4° C.), pulse 100, and respirations 30. Auscultation revealed harsh breath sounds and loud rales at all areas of the chest. It was considered that penicillin therapy should be instituted. He was accordingly given an intramuscular (deltoid) injection of 1 ml., equivalent to 300,000 units of the procaine salt, from the 10-ml. vial of the suspension preparation in current use, and from which similar amounts had been given to other patients with no ill effects.

In a matter of a few minutes, less than five, I was called to see the patient again; he was very distressed and apprehensive, was vomiting, and had a generalized skin rash, and his tongue was swelling quite rapidly and alarmingly. From the difficulty he had in breathing it was apparent that the mucous membranes of throat and pharynx were involved in a general oedema. The skin rash was progressing rapidly to a generalized urticarial reaction. The pulse, formerly full and regular, became almost imperceptible, with an occasional missed beat. An injection of 5 minims (0.3 ml.) adrenaline hydrochloride was given immediately, and ice to suck. This had little effect, and the patient had a convulsion. The dyspnoea and the swelling of tongue and pharynx were increasing alarmingly, making one contemplate speedy tracheotomy. A deep subcutaneous injection of 2 ml. 2.5% solution (0.05 g.) of "anthisan" was then given. This produced considerable relief of the condition in the course of about 15 minutes. The patient had a further convulsion about two hours later and required a further injection of 5 minims adrenaline hydrochloride. He perspired freely and was fairly comfortable. Penicillin therapy was not proceeded with: the chest condition was treated with sulphadimidine. This patient had had a course of ordinary aqueous penicillin on a previous occasion in hospital, without ill effect.

This is the first reaction of this kind that I have experienced in the course of a very large number of cases. The manufacturers point out that most reactions respond to antihistamine drugs, and the importance of keeping one of these preparations to hand while undertaking this method of penicillin therapy is worth emphasizing, in spite of the evident rarity of this severe type of reaction.—I am, etc.,

Galwally, Belfast. T. V. HUMPHREYS.

Fowl Pest

SIR,—Your annotation (January 20, p. 131) is surely in error when it says that there are no serological changes in conjunctivitis resulting from human infection with Newcastle disease. In the A.M.A. *Archives of Ophthalmology*, 1950, **44**, 573, is an article by A. H. Keeney and M. C. Hunter, "Human Infection with the Newcastle Virus of Fowls," where the specific point is discussed, and a case reported in which a significant rise in haemagglutination inhibition titre of the patient's serum was found a week after infection. The long-term study of the immune response is stated to be in preparation.

The authors also quote three further cases, from the 30 previously reported as clinically identified, which showed a definite rise in antibody titre. In none of these 30 was the virus recovered from the blood stream, but in the patient reported by Keeney and Hunter a viraemia was proved.—I am, etc.,

Ayr. W. O. G. TAYLOR.

Aspirin and the Adrenal Cortex

SIR,—Dr. J. B. Cochran, Mr. R. D. Watson, and Dr. J. Reid, in their article (December 23, 1950; p. 1411) on the production of a mild Cushing's syndrome due to aspirin, have suggested that this drug may stimulate, directly or indirectly, the formation of cortisone by the adrenal cortex. Further support for this view is given by my experiments on rats (M.D. thesis, Bristol, 1950).

Eighty adult male rats were given soluble aspirin (½ gr. or 30 mg. per 100 g body weight), 40 by intraperitoneal injection, 40 by stomach tube, and were killed at time intervals ranging from five minutes to 72 hours afterwards. Three histochemical tests were employed (Yoffey, J. M., and Baxter, J. S., *J. Anat.*, 1949, **83**, 89)—the Schultz test for cholesterol, and the plasmal and phenylhydrazine reactions. In both series of experiments all three tests gave roughly parallel results—namely, depletion of cholesterol or other stainable material within 30 minutes of administering the aspirin. The reticularis and fasciculata showed a marked depletion, while the glomerulosa was unaffected.

It is, of course, not clear from these experiments whether the aspirin acts directly on the adrenal cortex or indirectly via the anterior lobe of the pituitary. But, whatever the mode of action, there seems to be no doubt that in the rat it is a very potent one, and, judging by the report of Cochran, Watson, and Reid, it may on occasion, if not invariably, exert a powerful effect in man also.

Repeated doses of aspirin enabled one to follow, by means of the histochemical picture, the various stages of Selye's adaptation syndrome. Following the administration of aspirin daily for four or five days, the cortex passed from the stage of "alarm" to that of "resistance" and the histochemical picture returned towards the normal. However, when the aspirin was given for 10–14 days, the cortex passed into the stage of "exhaustion" and showed extreme depletion.

At the time these experiments were performed I hesitated to make any inferences from rat to man. The dose of aspirin employed in the rat, ½ gr. per 100 g. body weight, would correspond to a dosage in man of 350 gr. (22.7 g.). In addition there is, of course, the problem of species differences to be taken into account. It is therefore all the more interesting to find that even the very much smaller doses employed clinically may exert an appreciable effect on the adrenal cortex.—I am, etc.,

Bristol. FRANCES B. ROBINSON.

Treatment of Lumbar Disk Lesions

SIR,—I have read with great interest the communication of Dr. James Cyriax (December 23, 1950, p. 1434). But I would like to emphasize that pure malrotations of lumbar vertebrae can often so closely simulate disk lesions, having such similar symptoms, as to be mistaken for them.

During the last few years I have had a number of patients who have received the diagnosis of lumbar disk lesion and been advised to wear plaster jackets for prolonged periods, etc., in whom I have found nothing more than malrotations in the lumbar vertebrae, usually of the fifth on the sacrum, less commonly of the fourth on the fifth. The bony signs of these minor displacements (which are not present in disk lesions) have been mal-alignment of the spinous processes of the lumbar and sacral vertebrae, and elevation of one-half of the pelvis with the patient lying on her side. The treatment I have adopted in these cases has been first to administer manual vibrations in order to induce complete relaxation of the lumbar muscles; then, with the patient on her side, to make a sudden rotation of the trunk in the direction opposite to the one in which the malrotation has taken place. In many cases two manipulation treatments have been successful in replacing the malrotation, removing all signs of the bony irregularities mentioned, and coincidently causing the prompt disappearance of all the subjective symptoms. The actual reposition is entirely painless and the results nearly always permanent.—I am, etc.,

London, W.1. EDGAR CYRIAX.

Tar Burns: Traditional Treatment

SIR,—Under "Any Questions?" in your issue of January 27 (p. 203), we read with interest how to treat burns from hot tar and how to remove tar from the skin. Having worked in the North-east of Scotland, with its population largely engaged in shipbuilding, we have seen some such tar burns, and we followed the advice of a fisherwoman so afflicted to leave the burn and the tar alone. This is the traditional practice among these people. We have, since then, seen excellent results from this perfect dressing; it is sterile on application and presumably sterilizes the part it covers. It comes off by itself in due course like the tan of old.—We are, etc.,

Birmingham. PETER KONSTAM. SHEILA KONSTAM.

Silicone in Syringe Sterilization

SIR,—The ideal and only practicable method of syringe sterilization for hospitals is by hot air as recommended by the Medical Research Council in *War Memorandum* No. 15 (1945). There it is recommended that the barrel of the syringe should be "lightly lubricated with liquid paraffin, lightly rubbed in with the finger" before assembling, placing in a suitable test-tube, wrapping in "cellophane," and placing in

the hot-air oven at 160° C. It must be common experience that after repeated sterilization, and in spite of careful cleaning each time, this procedure is invariably followed by some degree of charring of the paraffin. This deposition of finely divided carbon is extremely difficult to remove and gives a discoloured syringe whose graduations may be difficult to read; and both patient and medical attendant may well resent the use of an apparently dirty instrument, or at least one that has been imperfectly cleaned. The main defect, however, is that in course of time the syringe tends to stick when used, and it is not easy to think of a more inconvenient or irritating event.

To overcome these difficulties we have tried out the use of silicones as lubricants. After trying several of these substances, we find that Silicone D.C. 550 (Albright and Wilson) is the most satisfactory agent. In practice, it is dissolved in methylated ether as a spreading agent, in the proportion of silicone 1 part to ether meth. 2 parts. The tip of the plunger of the cleaned syringe is dipped in this before insertion into the barrel and subsequent sterilization.

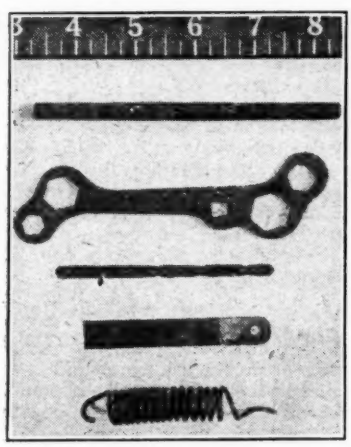
This particular silicone has a comparatively high boiling point and is unaffected at the temperature used for sterilization, and the greatly reduced number of carbon atoms in its molecule, as compared with molecules of aliphatic oils, makes charring virtually impossible under these conditions. Furthermore the water-repellent properties of silicones make for easier cleaning after use; and when the syringe is used for blood the coagulation is appreciably delayed, with obvious attendant advantages. This silicone is chemically inert and appears to have no effect on samples taken for bacteriological, haematological, or biochemical investigations. This small but important modification has given satisfactory results in routine use in our syringe service in the last few months.—We are, etc.,

G. H. DARLING.
Bristol. J. G. C. SPENCER.

Human Ostrich

SIR,—The following case may be of sufficient interest to merit publication.

A migratory labourer aged 24 years was admitted on May 21, 1948, complaining of generalized abdominal pain, temperature 100° F. (37.8° C.), pulse 116, respirations 22, bowels regular, some frequency of micturition but without pain. Inspection showed a recent abdominal scar, which was from an appendicectomy five weeks before. Bimanual palpation disclosed a tumour low down and mesial to McBurney. The lower abdominal wall felt tumid and thickened but did not pit. Suspecting that a sponge or other foreign body might possibly have been overlooked at previous operation, it was considered prudent to postpone further surgery until contact could be established with the previous operator. However, before this could be done symptoms of generalized peritonitis became much more marked and rendered emergency operation imperative. The abdomen was opened in midline below the umbilicus. The parietal peritoneum was found to be grossly oedematous, and a bunch of small bowel was adherent to it. Exploring gently with the finger, I found what I thought at first might be a hard rubber tube inside the ileum about 2 ft. (60 cm.) from the caecum. Opening the thickened ileum and gently inserting a finger, I encountered first what I thought was the "eye" of a forceps. It proved, however, to be the bicycle spanner depicted in the photograph. Exploring further, my finger was caught by one end of the tension spring also shown. The lower end of this spring caught in the edge of the opening in the ileum, and while held thus the steel twist drill and the bicycle axle were brought to the surface. The condition of the patient precluded more exhaustive search, the ileum was closed, and the abdomen drained.



Some hours later, wishing to confirm that I had removed all the ingested foreign bodies, I questioned the patient, who, *inter alia*, said, "I am afraid there is a bit of a hacksaw there yet!" His post-operative condition precluded immediate radiography, but an attempt was made to wrap up the remaining foreign body by administering cotton-wool sandwiches, etc. Later the piece of saw blade was visualized, and finally passed per anum comfortably wrapped up in the cotton-wool.

It transpired that a huge double-threaded bicycle nut (the one that joins the front fork to the stem) had been removed at the previous operation.

I have no further comment to make, save that the patient made an excellent recovery and that observation since the date of discharge failed to disclose any abnormality, mental or physical.—I am, etc.,

Cavan, Eire. J. C. MCMULLIN.

Methoin in Epilepsy

SIR,—In his interesting paper (January 13, p. 64), Dr. D. P. Jones discusses the value and limitations of methoin in the treatment of epileptics attending out-patient clinics. Our experience in the treatment of 20 patients in this mental hospital is in general agreement with his findings. All our cases were suffering from epilepsy with behaviour disorder and had failed to improve on the usual drugs. In the majority of cases methoin led to a marked decrease in the frequency and severity of fits. Irritability and impulsiveness also diminished, making nursing much easier. These effects were seen even on such small doses as 0.3 g. daily, and in no case have we used more than 0.9 g. daily.

Our early enthusiasm was, however, damped when a severe morbilliform rash occurred in a woman of 62 during the third week of treatment, when a dose of 0.3 g. daily was reached. Her skin condition cleared up when the drug was discontinued. A second case indicating the high toxicity of methoin was of a more severe nature. A chronic deteriorated epileptic aged 36 had been treated with phenytoin for nearly a year without much improvement. The drug was then gradually replaced by methoin. At the end of the third week he was observed to be pale, and blood examination showed that he had developed aplastic anaemia. Despite regular blood transfusion during the past eight weeks, there is as yet no sign of recovery of haemopoietic function.

In view of this experience, similar to American reports and Dr. Jones's case, it appears that the high toxicity of methoin will restrict its value in in-patients where prolonged medication is required and the social benefits from the diminution of the number of fits are relatively small.—We are, etc.,

J. T. LEYBERG.
Macclesfield. R. M. YOUNG.

Congenital Malformations

SIR,—Your annotation (January 20, p. 130) is misleading on three points.

First, Murphy[1] is quoted as stating, "The chance that any couple will have defective offspring is 1 in 200." This statement has little meaning unless related to size of family, and we cannot find it in Murphy's book. He does, however, say (p. 66), "It was found that about 1 child in every 213 in the general population presented a congenital defect." This figure of 1 in 213 is much too low on any definition of congenital defect, and later in the same annotation attention is drawn to the finding of Record and McKeown[2] that the incidence of major congenital malformations of the central nervous system alone was 0.59%, more than 1 in 200. This is a point of some importance, since uncritical acceptance of this figure led Murphy[1] to suggest that placenta praevia is followed by an abnormally high incidence of malformations.

Second, Murphy is quoted, without comment, as stating, "The likelihood that a second malformed child will be born to parents who have had one is increased 20–25-fold." On Murphy's reckoning this implies that the chance that each

subsequent child will be affected is between 1 in 10 and 1 in 8. This gives much too gloomy an outlook. Of 117 mothers at a London maternity hospital who gave a history of a previous pregnancy resulting in a malformed child, only three had a malformed child.[3] However, any estimate of the risk based on malformations in general is of little value, since it appears at the moment that it is only the same or similar malformations that tend to recur with undue frequency in later children and that the risk varies in different types of malformation. None of the common malformations recur with a frequency as high as 1 in 10. Your annotation quotes Record and McKeown's findings of about 1 in 35 for central nervous system malformations, but does not make clear that it is only the risk of the same and other central nervous system malformations that is raised and not the risk of deformities of other parts of the body. For talipes equino-varus the risk is of about the same order, while that for congenital heart disease is very much less. The only deformities with a high rate of recurrence are those determined entirely by single dominant or recessive factors, and these are rare.

Third, Murphy is quoted as stating, "The hazard of malformation increases with the age of the mother, rising progressively year by year after the mother has passed 30." Murphy arrived at this conclusion by an unsound statistical method[3 4] and there is evidence that maternal age has little effect on the incidence of deformities except in the case of mongolism.

Finally, the animal experiments, such as those of Warkany mentioned in your annotation, though of great theoretical interest, must not be taken as indicating that similar agencies necessarily play any part in causing human deformities. For example, there is no good evidence that malnutrition causes deformity in man.—We are, etc.,

C. O. CARTER.
J. P. M. TIZARD.

The Eugenics Society, London, S.W.1.

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[1] *Congenital Malformations*, 1947. Philadelphia.
[2] *Brit. J. soc. Med.*, 1950, **4**, in the press.
[3] Carter, C. O., *J. Obstet. Gynaec. Brit. Emp.*, 1950, in the press.
[4] Stevenson, S. S., Worcester, J., and Rice, R. G., *Pediatrics*, 1950, **6**, 37, 208.

New Scholarships in Public Health

SIR,—In recognition of the services of Sir George Elliston, who has just demitted office as its chairman after eleven years' tenure, the board of management of the London School of Hygiene and Tropical Medicine has decided to offer two scholarships of £150 each, with free tuition, for students taking its course for the Diploma in Public Health commencing in October, 1951. Official intimation will be found in the advertisement columns. These are additional to the Bygott Scholarships, awarded by the University of London, also tenable at this school, about which official notification will appear later.

The Board hopes that the Elliston scholars will eventually join the preventive services in the United Kingdom, the number of recruits to which has been seriously reduced by the discrepancy existing between the emoluments offered and those obtainable now in other branches of the medical profession. We hope that many more of the medical officers of health of the future will become the pivotal points of the medical services of their areas. All thinking people deplore the increasing tendency for each section—domiciliary, hospital, and preventive—to develop and function as separate entities. The medical officer of health with the proper outlook and background should, we think, be the co-ordinator: this implies a very adequate clinical training, and we hope that men of good quality will give careful consideration to adopting community health as their career.

The modern course for the D.P.H. is much more a cultural discipline than a technical training, and there are few young medicals who would not derive great benefit from it whatever their ultimate aim.—I am, etc.,

ANDREW TOPPING,
Dean.

London School of Hygiene, W.C.1.

POINTS FROM LETTERS

Psychology in the D.P.M.

Dr. J. B. G. SMITH (Sutton, Surrey) writes: . . . I feel psychology does need some standardization, especially from the textbook point of view . . . no two examiners or tutors will recommend the same books. . . . D.P.M. psychology, too, is complicated by the varying emphasis shown by examiners. How is the unfortunate candidate to know who are the ardent devotees of Freud, Jung, or Adler and so will exhibit a bias towards their respective doctrines ?

Dr. A. K. GRAF (Brentwood, Essex) writes: . . . I cannot agree with the views expressed by Dr. A. Folkson (January 20, p. 140). . . pure psychology (is) a most stimulating and sound basis for the understanding of preclinical and clinical aspects. . . . Much does not seem relevant to clinical work at first, but as time and experience progress and the psychiatrist learns to deal with all the manifold aspects of his specialty he will find in time opportunity of using most of the academic knowledge he has gained in studying psychology for the D.P.M. When he reaches consultant status and has to work with non-medical psychologists he will sorely realize how deficient his knowledge in their specialty is, and, humiliated by the clinical relevance of such knowledge, he will at a late age hurry to make up his shortcomings in pure psychology by renewed reading and study of academic psychology.

Athlete's Foot

Dr. T. B. RANKINE (Liverpool) writes: I have had some personal experience of this affliction while resident in the West Indies, in which climate athlete's foot tends to be a considerably more severe disease than is the average case met with in Britain. While the treatment outlined in the article by F. R. Bettley (January 6, p. 28) may be adequate for these cases I feel that it may well be found to be disappointing in the more severe case—and it would certainly fail to arrest the progress of any but the most trivial case in a more tropical climate. The basis of treatment is in keeping the affected skin as dry as possible. If Whitfield's ointment be merely spread on the socks the fungus will soon thrive on the sodden skin bathed in the sweat accumulating under the layer of ointment. I have found that the most effective regime was as follows: (1) The feet are kept as cool as possible, preferably only open sandals being worn over thin woollen socks. (2) At night—or in the evening if no more walking is to be done—the feet are bathed in a basin of hot water, carefully cleaned, and the loose scales removed. Then follows thorough drying, paying particular attention to the interdigital clefts. The feet are now swabbed with spirit—this may prove a trifle painful but it is by no means unbearable—and then allowed to air for a period. The ointment is now applied and thin socks worn. (3) In the morning the feet are swabbed with spirit till all moisture (and this includes the ointment) is removed. The feet are now liberally dusted with an absorbent powder—the pulv. acid. salicyl. co. of the *B.P.* is a good preparation for the purpose—using the sock as a powder-puff. Plenty of powder must be used, and in severe cases it may be wise to shake a further quantity into the shoes themselves. Obviously this process may be repeated in the course of the day, a fresh pair of socks and shoes employed, etc., according to circumstances. . . . Another important point is that cure is never permanent, for the fungus seems to get into the footwear and there lodge until the next occasion that hot damp feet are offered to it. It is therefore a wise plan for the patient to repeat the morning dusting (the spirit is not now needed) for the rest of the summer and to resume the powdering at the first sign of itching and redness between the toes The sheet anchor of the treatment is the absorbent powder. Whitfield's ointment need be employed only when a rapid response is not obtained with spirit and powder.

Corrections

Dr. R. BOWERS writes: In my article on haemangiomatous naevi (January 20, p. 121), Case 41, in the moderately improved group, was treated for nearly two years, not one year as stated. Thirty paintings in one year would have been excessive, especially for a child aged 5 months.

In Dr. W. N. Leak's letter (February 3, p. 246) on "Foetal Asphyxia" the last sentence of paragraph 2 should read ". . . the cerebral (*not* central) blood of the foetus . . ." and the first sentence of paragraph 4 ". . . suffering from pure nervous shock, while surgical (*not* nervous) shock is mainly . . ."

In "Diagnosis of Aortic Stenosis," by Dr. D. Lewes (February 3, p. 211), in Table IV, under "pulse volume" in Cases 14 and 16, for "dicrotic" read "anacrotic."

Obituary

O. H. MAVOR, C.B.E., LL.D., M.D.

Dr. O. H. Mavor, the Glasgow physician who, under the pen-name of James Bridie, became one of the most respected dramatists of the day, died on January 29 in the Edinburgh Royal Infirmary, to which he had been admitted with symptoms of cerebral haemorrhage.

Osborne Henry Mavor, whose father was an engineer, was born at Pollokshields, Glasgow, on January 3, 1888. He attended a number of Glasgow schools, including Glasgow High School and Glasgow Academy, which he left to take up the study of medicine. His career as a medical student was a chequered one, but he soon became prominent in undergraduate circles. He was one of a band of bright youths, some of whom, like Walter Elliot, Tom Johnston, and James Maxton, won political fame, while others achieved the less spectacular distinction of a professorial chair. Among them Mavor's distinctive genius soon attracted notice. He contributed prose and verse to the Glasgow University magazine, of which he later became editor, while his sketches revealed him as a born artist. The "daft" little songs he composed and sang were sparkling turns at many a social gathering, and his caricatures of his medical teachers are still treasured by their possessors. He graduated M.B., Ch.B. in 1913, and then worked for about a year as house-physician and house-surgeon in the Glasgow Royal Infirmary. On the outbreak of the first world war he joined the R.A.M.C., and within three months was in France with a field ambulance. In 1917 he was sent out to the Middle East, and served in Mesopotamia, India, Persia, Transcaucasia, Constantinople, and Baku. It was in these countries that he gained much material for his biblical plays.

Barratts, London

When Mavor returned to civilian life he went into practice at Longside, Glasgow. He was appointed extra physician at the Sick Children's Hospital Dispensary, and in 1923 he decided to set up as a consultant. He became F.R.F.P.S.Glas. in 1921, and graduated M.D. (with commendation) in 1929. For a time he held the post of professor of medicine at Anderson's College, and he was also a visiting physician to the Victoria Infirmary. His students found him an unconventional if not an eloquent teacher. It was not until 1934 that he abandoned medicine for literature and the theatre. Even so, he never gave up his interest in medicine, as readers of his "Study of the Umbilicus" (*British Medical Journal, Supplement*, 1939, 1, 245) will remember. This fascinating discourse, which he gave as the presidential address to the Southern Medical Society of Glasgow, ended with these words: "The doctor can try to do justice; he must love mercy; and it is incumbent on him to walk humbly with his God." In the second world war Mavor served again with the R.A.M.C., and, as Eric Linklater records in his *The Road to Adventure*, he was in a hospital ship which evacuated the wounded from Andalsnes and other parts of Norway. He was already well over age when he rejoined, and he had only with difficulty persuaded the authorities to commission him again. He returned to civilian life in 1942, being granted the rank of major.

Mavor always remained a faithful citizen of Glasgow, though he had some great successes with his plays in London and elsewhere. *The Anatomist*, produced at the Westminster Theatre in 1931, ran for 127 performances. Glasgow University bestowed the honorary degree of LL.D. on him in 1939, and he was awarded the C.B.E. in 1946. His play *Gog and Magog* gained the Bernard Shaw Birthday Prize last year. He was a member of the council of the League of British Dramatists, of the Council for the Encouragement of Music and the Arts (the Arts Council), and a director of the Scottish National Theatre Society.

He married Miss Rona Bremner, who survives him together with his son, who is a doctor. His other son lost his life in the last war.

G. F. writes: As James Bridie, Mavor was a prolific writer whose incalculable and provocative genius alternately delighted and perplexed his audiences and provided rich matter of debate for the critics. In much that he wrote his professional training was turned to account. He was a man of many interests, and the representatives of the university, medicine, the city, the stage, and literature who were present at his memorial services bore witness to the heavy loss which his death means for many circles. His life and his opinions were characteristically presented in his autobiography *One Way of Living*. Mavor was no orator, but he was an excellent story-teller. In discussion he was prone to punctuate a run of mumblings with barked-out negatives, for, while he was generous with help and advice to others, he went his own dour way. Personally he was a tallish, burly Scot, who peered out at life with puckishly critical eyes. An odd mixture of brusqueness and shyness, he was a difficult man to get to know, and a stranger was often uncertain whether he was witnessing a touching display of modesty or having his leg pulled. But those who were privileged to know Mavor well knew him to be a kindly and deeply lovable man.

Mr. Ivor Brown has kindly written this appreciation of Dr. Mavor's work as a dramatist: The other Dr. Mavor, James Bridie—also a doctor, being honorary LL.D. of Glasgow University—was a dramatist with a rare gift of fluency. He poured out plays—or at least the beginnings of plays: it was obvious that he sometimes trusted for his third act to an inspiration that did not come. "Only God can write third acts," he said. And God was not always at his side.

But how admirable in wisdom, as in wit, Bridie could be when he sustained his original impetus and finished as strongly as he began. He had three main sources for subject-matter: they were his own medical experience, his Scottish background, and his first-war experiences in the Middle East which carried him into the world of biblical and apocryphal legend. The last of these provided what is perhaps the most abidingly popular element of his work; repertory theatres will never cease to play *Tobias and the Angel* and *Jonah and the Whale*. Scotland and its creeds and cranks gave him some of his successes, especially with the satanic incursion into Highland Calvinism of *Mr. Bolfry*. But perhaps Bridie

was at his best when he was mixing Caledonian and whimsical matters and translating them into an idiom for laymen and even Londoners to understand.

He began with a medical play, *The Switchback*, concerning the career of a much-publicized researcher and discoverer. This was given by Sir Barry Jackson at the Malvern Festival, of which Bridie remained always a loyal supporter; his was a figure almost as well known and beloved there as was that of Bernard Shaw. Later came the engaging study of *The Anatomist*, the one-eyed, hideous, dandiacal, self-willed, and dedicated Dr. Knox, whose association with Burke, Hare, and body-snatchers (for purely surgical reasons) did not quite ruin him; his free-thinking did. Then came *The Sleeping Clergyman*; the title referred to God, who may be thought to doze while men's destinies are made. Part of the subject was heredity and the futility of trying to breed for perfection in the human stock. Genius is our necessity, and genius may grow anywhere, at any time, with freakish antecedents. Mankind is all right—if we find it something decent to do. God is not a bad biologist in the long run. That is the general drift of a play which is possibly Bridie's best.

Bridie was sceptical of all professional and professorial law-giving; but while he loathed the confident assumptions of certainty in others, he had a good conceit of his own talents and obstinately disregarded criticism. He combined the gentlest manner with the stiffest neck of any man in my own fairly wide acquaintance of writers and artists. His muttered conversation was charming, when it was audible, which was not always; his kindness to colleagues and beginners as great as his hospitality and his relish for long nights of chatter in congenial clubs.

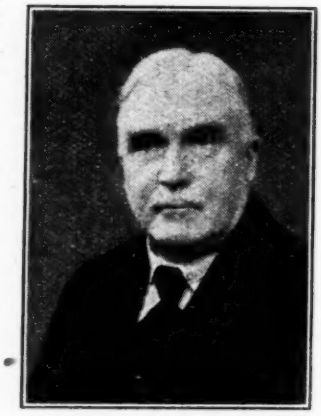
His kind of drama, wayward in theme and treatment but never for a moment pompous or heavily doctrinal, was rooted in his own affection for all sorts and conditions of men. He had met them so widely in war and peace, in hospital and hotel, in august clubs and in queer company—he had met them and liked them as well as watched them. There lay his strength. He enjoyed all the humours and savours of life. Through lack of a sustained story his plays occasionally faded; his characters were more abiding stuff. When a plot, as well as his ideas and his persons, was there to help him he was irresistible.

JAMES SWAIN, C.B., C.B.E., M.D., F.R.C.S.

Mr. James Swain, emeritus professor of surgery in the University of Bristol, died at his home in Easton-in-Gordano, Somerset, on January 6, at the age of 88. He was one of a small number of surgeons who made a great mark in Bristol and the west of England in the early years of this century. He came to Bristol when Greig Smith was introducing modern surgery: for a few years he acted as his assistant, and when Greig Smith died at an unexpectedly early age his mantle descended on Swain, who wore it worthily for nearly a quarter of a century.

Swain was originally from Hertfordshire, and he had a brilliant career as a student at the Westminster Hospital, where he gained an entrance scholarship in 1879, following this by winning the Chadwick Prize and the Bird Medal and Prize. He qualified in 1883, and after holding resident appointments at the Westminster he graduated M.B. with honours in 1885. Two years later he proceeded M.D. In 1887 he came to the Bristol Royal Infirmary as house-surgeon and senior resident officer. Some of his higher qualifications—the F.R.C.S. in 1889 and the M.S. in 1890—were gained while he was in residence in Bristol. When a vacancy occurred in 1892 for an assistant surgeon he was the outstanding candidate and was elected to the post.

Professor J. A. Nixon writes: At the time of Greig Smith's death in 1897 Swain had made a reputation as a sound hard-working surgeon who never spared himself in working for his patients in private or in hospital alike. Although he travelled countless miles by train and carriage in the south-west of England, consulting and operating, he never allowed private calls to interfere with his hospital duties. He succeeded Greig Smith as professor of surgery in University College, Bristol, in 1897, holding a dual office with Charles Morton, a surgeon from the Bristol General Hospital. Although there was ridiculous rivalry at that time between the Royal Infirmary and the General Hospital, Swain and Morton worked harmoniously together. One of Swain's great assets was his indisposition to quarrel. Yet he was a man of strong personality and firmly held opinions, and he usually got his way without brawling. He lived in difficult times. He saw his own path clearly. He practised throughout his career as a pure consulting surgeon, and, like many another first-class surgeon, he was a very good physician. But he happened to be on the Infirmary staff at a time when specialism began to appear. Richardson Cross was already established as an ophthalmic surgeon and was above any opposition. P. Watson Williams, an assistant physician, and Walter Swayne, an obstetrician, were both on the Infirmary staff. The former became a disciple of Sir Felix Semon and presently began to practise as a nose and throat surgeon. This met with opposition from some of the surgeons, who did not see how a physician could be allowed to perform operations. Walter Swayne met with similar opposition when he began performing abdominal operations for gynaecological conditions.



Many bitter disputes raged in the faculty meetings of the Infirmary. The older surgeons felt it intolerable that their fields of surgery should be invaded. They were, however, at a disadvantage. The senior surgeons had neither university degrees nor the F.R.C.S. They were, without exception, engaged in general practice. The younger ones, Swain and Carwardine, were graduates of London University and both F.R.C.S. of England. James Swain, without talk, quietly encouraged both the rising specialists. He took a very definite side in the matter and did not waste time in arguing. It was evident that if he supported Watson Williams and Swayne opposition would fail. It failed in the main because of the wisdom with which James Swain held his tongue. He sympathized with the new development and realized that it was coming to stay. It came all the quicker because of his solid support.

In 1909 Swain was elected president of the Bristol Medico-Chirurgical Society and in the same year became

professor of surgery in the newly chartered University of Bristol. Besides being the author of numerous papers on surgical subjects in this and other journals, he was associate editor of the *Bristol Medico-Chirurgical Journal* from 1897 to 1924 and editor of the sixth edition of Greig Smith's *Abdominal Surgery*. When the 1914 war broke out he was appointed consulting surgeon to the Southern Command, with the rank of lieutenant-colonel, R.A.M.C. During the whole war he travelled extensively on his visits to military patients in the south-west of England. He was mentioned in dispatches and awarded the C.B. (military), together with the rank of colonel, A.M.S. Between 1917 and 1919 he paid several visits to the Armies in France and Flanders, and was a member of the Inter-Allied Congress on Treatment of Wounds in War held in Paris. These services overseas were recognized by the award of the C.B.E. (military) in 1919.

He retired from the chair of surgery in 1920 and from his Infirmary post in 1922, being made emeritus professor of surgery and honorary consulting surgeon to the Bristol Royal Infirmary. He retired at once from private practice and in 1924 went to live at Easton-in-Gordano in Somerset. Swain knew how to relax, and, while not devoted to hobbies, had many interests. He loved foreign travel, especially in Switzerland, and for many years took part in Gilbert and Sullivan operas in the Clifton Operatic Society. His rendering of the major-general in the *Pirates of Penzance* survived as a memory for a long time. He was made a J.P. for the county in 1929, and sat for many years as a magistrate at the Long Ashton court. In 1899 he married Hilda, daughter of Dr. A. J. Harrison, of the Bristol General Hospital. She survives him with a son and daughter, to whom we offer our deep sympathy.

W. E. BARNIE-ADSHEAD, F.R.C.S., F.R.C.O.G.

Mr. W. E. Barnie-Adshead, the well-known Birmingham gynaecological surgeon, died in the Birmingham General Hospital on January 26 at the early age of 49.

William Ewart Barnie-Adshead was the son of Alderman P. W. Adshead, twice mayor of Dudley. He was a student at Birmingham University, graduating B.Sc. in 1920 and M.B., Ch.B. in 1923. He played a very active part in reviving athletic and social activities at the university after the first world war, and he was president of the University Medical Students' Society. He was outstandingly good at games: he captained the cricket, Association football, and tennis teams of the university, and played cricket for Worcestershire and football for Aston Villa, the Corinthians, and England. After qualification he held a number of resident appointments at the Queen's, Women's, and General Hospitals in Birmingham, and then came to London to continue his postgraduate studies. He became a Fellow of the Royal College of Surgeons of England and of Edinburgh in 1926, the year he was appointed assistant gynaecological and obstetric surgeon at the Queen's Hospital, Birmingham. In 1929 he joined the staff of the Women's Hospital, and eventually succeeded Mr. Lewis Graham in 1934 as head of his department. In 1938 he was elected a Fellow of the Royal College of Obstetricians and Gynaecologists, of which he was later a member of council. He was a lecturer and examiner in the University of Birmingham, and assistant to the professor of gynaecology and obstetrics. For a number of years he served on the Medical Students and Newly Qualified Practitioners Subcommittee of the Organization Committee of the B.M.A., and from 1930–1 he was joint honorary secretary of the Birmingham Branch. After the last war he was mainly responsible for reviving the Midland Obstetrical Society, of which he was president in 1938–9.

Professor Hilda N. Lloyd, P.R.C.O.G., writes: Barnie-Adshead has gone into the shadows, and it is difficult to realize that we shall see no more that lovable debonair figure and hear no more his delightful lisp. He was a typical English gentleman, a sportsman, and the most loyal of friends.

[Whitlock, Birmingham

Adshead had a flair for ball games, and as time went on he turned to golf as a medium to chasten the aspiring talents of his younger colleagues. Into his everyday professional life he carried the same spirit of sportsmanship and skill. He loved his work and valued his leisure. His courage never failed him, and in the twilight hours of his relatively short life he showed us all how suffering can be a mirror to reflect the steadfast faith that is in such a man. During the time I had the honour of his friendship I have never known him speak ill of anyone—his friendly, genial soul called all men friends. Of his professional skill there is no need to write: he was a real surgeon in all the meaning of that honourable title. He was a natural leader of men, and but for the slight impediment in his speech, about which he was perhaps too sensitive, he would have made his mark in public life. He was probably never aware of the great affection his students had for him. His family life was intensely happy, as would be expected of such a man. His two sons will carry with them into the future the abiding memory of a father upon whom to mould themselves. To his wife our hearts go out in her loneliness, and we pray that strength may be given to her in her need.

Dr. James F. Brailsford writes: With the passing of Barnie-Adshead Birmingham has lost its most popular citizen. All will mourn the loss of a great doctor, friend, and sportsman at an early age. His charm with his patients, his friends, and his colleagues was outstanding. Perhaps it was because of his perfect natural physical abilities that he was above all the misfortunes of ambition. The affection of his patients, his successes in his surgery, came as naturally as in his sport—for he was a first-class sportsman in football, cricket, golf, and tennis. His counsel was at all times thoughtful and free from all bias, and his happy outlook brought good-fellowship where there might have been estrangement. His memory will always be cherished by those fortunate enough to be associated with him, particularly those of us who were his fellow students and shared his confidence. In the prime of his life his astounding courage in facing recent evidence of the inevitable will always be an inspiration.

C. O. STALLYBRASS, M.D., D.P.H.

Dr. C. O. Stallybrass, until 1948 deputy medical officer of health of the city and port of Liverpool, died at the Clatterbridge Hospital, Cheshire, on January 28, aged 69.

Clare Oswald Stallybrass was born in Wallasey, the son of the Rev. W. C. Stallybrass, and was educated at Birkenhead School and the University of Liverpool. He qualified in 1905, and graduated M.B., B.S. at London University two years later. After serving as house-surgeon and house-physician at the Liverpool Royal Infirmary, he occupied a resident post at the Maternity Hospital, where in 1907 he established a medical clinic for infants on their discharge. Early on in his career he began to display an interest in preventive medicine which was to prove the predominating enthusiasm of his life: this showed itself when he accepted a post at the Parkhill Fever Hospital in 1908 and was appointed assistant medical officer in the Liverpool port medical service in 1909. He proceeded M.D. in State Medicine in the following year. His career in Liverpool was interrupted during the 1914–18 war, when he served in the R.A.M.C. For distinguished service to the Serbian Army during a severe epidemic of typhus in that country he was awarded the Order of St. Sava. Returning to England at the end of the war, Stallybrass was appointed, in 1919, an assistant medical officer of health in the Liverpool public health department, and he then began his long career of service to the city which was destined to last for more than 30 years.

We are indebted to Professor W. M. Frazer for the following account of Dr. Stallybrass's work in Liverpool: For a considerable time Stallybrass shared a room at the municipal offices with Dr. A. A. Mussen and the late Dr. W. Hanna. These three, under Professor E. W. Hope, who died a few months ago, formed a very strong team, and it is to their devoted work that we owe the immense progress in communal medicine which took place during the next few years in Liverpool. Stallybrass was the epidemiologist of the team. His nascent interest in this subject was no doubt stimulated by his experiences during the war, and he had an unrivalled field to work in at Liverpool, with its slums, docks, and casual labour. Early in the 'twenties he began the practice of immunizing children against diphtheria, and achieved some success with the immature antigens then at his disposal. His work in Liverpool formed the basis of practical experience for his *Principles of Epidemiology*, published in 1931. This was an important book. It was the first systematic treatise on epidemiology written in this country, and its publication established Stallybrass's reputation as an international authority on this subject. He collaborated with Hope (and later with the present writer) in the production of a *Textbook of Public Health*, which has passed through many editions, and with Hope and Hanna in the compilation of *Industrial Hygiene and Medicine*.

In 1933, after the retirement of Dr. Hanna, Stallybrass was appointed deputy medical officer of health of the city and port of Liverpool. The Local Government Act, 1929, had transferred the boards of guardians' hospitals to the major local authorities, and Liverpool's share brought its total of hospitals and institutions up to 19, comprising nearly 10,000 beds. During the 'thirties Stallybrass's activities were concentrated upon the administration of this hospital system, and it was then that he performed his most useful official work: the great ability and enthusiasm which he always brought to bear upon his public health duties were devoted to the improvement of the Liverpool hospitals and their associated services. In this work he was helped by his many contacts among the medical profession of Liverpool and by the great esteem and affection in which he was held by all classes of the community. The success of his labours was clearly shown between 1939 and 1945 in the great part played by the Liverpool hospitals in the war effort.

Stallybrass's interests were very wide, and he could (and often did) discourse upon archaeology, geology, astronomy, philately, mountaineering, psychology, music, and many other topics. He had an immense love of and concern for humanity. More than most men he might justifiably have echoed the saying of Terence—*Homo sum; humani nihil a me alienum puto.* During the many years of his interesting life in Liverpool, filled with every diverse kind of intellectual pursuit, he became a member, or treasurer, or president, at one time or another of most of the city's learned societies. His interest in them, once gained, never flagged. His abiding interest, for more than 40 years, was in the Liverpool Medical Institution, of which he was president in 1935, and in the many activities, both central and local, of the British Medical Association, in which he held many offices, including that of Representative of his Division at many Annual Meetings. He was a member of the Public Health Committee and of the committee which drew up the *Charter for Health*, and at the Annual Meeting of the Association last year he was president of the Section of Geriatrics. At this same Meeting he was selected to give the public lecture, and he chose as his subject "Epidemics Old and New" (reported in the *Journal* of July 29, 1950). In this he paid a moving tribute to those who in the past had fought to reduce the ravages of epidemic disease, and finished with a stirring appeal for an all-out attack on tuberculosis. For many years a member of the Society of Medical Officers of Health, he was an ex-president of the North-western Branch. Apart from his books, his literary output, on a wide range of public health subjects, was very large. Articles, papers, and letters of high quality came frequently throughout the year from his untiring pen. Many were published in this *Journal*: the last was a letter on the subject of tuberculosis which appeared only five weeks ago.

Stallybrass was senior lecturer in public health administration at the University of Liverpool for many years, and his great knowledge and experience, joined to his power of exposition, made him a fascinating teacher of students. In 1950 the university conferred upon him the honorary degree of Doctor of Medicine. After his retirement from the service of the corporation in 1948 he undertook a revision of his *Principles of Epidemiology*, played a large part in the founding of the Merseyside Marriage Guidance Council, and became chairman of the Liverpool Children's Hospital Management Committee. Life and humanity still interested him even up to the day of his death.

As the writer has reason to know, Stallybrass was a most loyal colleague and friend. The one or two disappointments which he experienced in his career did not embitter him or affect the equanimity of his constant spirit. He possessed his own deeply rooted conceptions of his duty to his fellow men, and within the wide scope of his opportunities did his best to serve them. The public health service of this country has seldom in its long history possessed a member who brought to it so

much constancy and loyalty and such a measure of devotion and ability as did C. O. Stallybrass.

He married Irene Stallybrass (Wetherhead), the widow of his brother, and there were two sons of the marriage. His was an especially happy family life.

R. J. BLACKHAM, C.B., C.M.G., C.I.E., D.S.O., M.D.

Major-General R. J. Blackham, for many years the only representative of the medical profession on the Court of Common Council of the Corporation of London, died on January 23 at his home in Sussex, aged 82.

Robert James Blackham was born in Belfast in 1868, the son of Dr. W. S. Blackham. He studied medicine at Dublin, qualifying in 1892. Three years later he joined the Army Medical Staff, and served with the Tirah Field Force in 1897–8, and also with the Khyber Brigade. He was on plague duty in the Punjab during the first year or two of this century. In these early years he continued to extend his knowledge in many directions. He joined the Middle Temple in 1903, and passed the Bar Final Examination some years later without attending a lecture. In 1905 he took the D.P.H. He was keen on ambulance work, and travelled and lectured for the St. John Ambulance Brigade, of which in later years he became assistant commissioner. He was close at hand and gave first-aid when the Viceroy of India (Lord Hardinge) was seriously injured in Delhi by the explosion of a bomb, and from 1912 to 1914 he was on the staff of the Viceroy. He was awarded the Kaisar-i-Hind medal in 1911 and appointed C.I.E. in 1913.

During the first world war Blackham served first as D.A.D.M.S. to the 33rd Division, but later, in France, as A.D.M.S. to the 23rd Division. He was promoted colonel, mentioned five times in dispatches, and, in 1917, awarded the D.S.O. Towards the end of the war he became D.D.M.S. of the 11th Corps. He was created C.M.G. in 1918 and C.B. a year later. Besides being awarded the French Croix de Guerre with palms and star, he was also made a Chevalier of the Legion of Honour. During "the troubles" in Ireland he was A.D.M.S. of the Dublin district. Despite his very active military life Blackham found time to improve his professional qualifications, for he became F.R.F.P.S.Glas. in 1914, M.R.C.P.Ed. in 1916, and he proceeded M.D. N.U.I. in 1918.

On his retirement from the Army in 1923 Blackham settled in the Temple and practised in the chambers of Mr. Travers Humphreys (later Mr. Justice Humphreys), who was at that time senior Treasury counsel at the Central Criminal Court. In 1925 he was elected to the Court of Common Council of the Corporation of London, and in 1927 he became clerk of the Worshipful Company of Glaziers and Painters of Glass. For his very valuable services to the company he was elected an honorary assistant in 1949. He was also a liveryman of the Apothecaries' and Needlemakers' companies, and a Knight of Grace and Member of Chapter General of the Order of St. John of Jerusalem. He served on the Court of Common Council for 25 years, and was Under-sheriff of the City of London in 1935–6. Among his numerous duties was that of commandant of the City of London police reserve. During the second world war Blackham served the Army once again, this time on the Medical Personnel Priority Committee, and was promoted major-general in 1941.

Few men could have had wider interests or taken such an active and important part in diverse affairs. Blackham was the honorary convener for many years of the annual professional nurses' and midwives' conference, and he served on the council of the Royal Institute of Public Health. He wrote many books, including textbooks which were translated into Indian dialects. *Incomparable India* was published in 1933, and *Woman: in Honour and Dishonour* in 1936. In a recent issue of the *Army Medical Services Magazine* there was a note about Major-General Blackham's work for the Worshipful Company of Glaziers and Painters of Glass. It ended with these words: "The Royal Army Medical Corps should be proud of the record of this distinguished and gallant officer, who has been as successful in his civilian career as he has been in the Corps."

Dr. B. T. Parsons-Smith writes: All who were fortunate enough to know him will have been grieved to hear of the death of Robert Blackham, and his obituary notices have testified to the very warm regard in which he was held, not only by his professional colleagues, but also by his numerous non-medical friends. As one who has valued his friendship for upwards of 30 years, I now pay a very affectionate tribute to his memory. In addition to his attractive personality, Blackham was a man whose long and distinguished career was characterized by his kindly nature, his enthusiastic approach, and his unfailing sincerity. Having had a lengthy period of public service in this country and abroad, Blackham acquired a fund of experiences to which he attached practical value and of which his numerous publications afford a permanent record. His most noteworthy quality was his high sense of duty, and, whether it was in the Army, in his civil appointments, in Freemasonry, or other of the various important offices which he filled, his capacity for leadership and his administrative skill proved to be of outstanding value. Blackham's legal training added materially to the scope of his personal judgment and to his general outlook on affairs. In conversation he was dignified, impressive, and unhampered by convention; he was skilled in the art of discrimination, he expressed his opinions with a sincerity which made it difficult for his opponents to take offence, his advice was founded on sound convictions, and he achieved a high reputation as a fluent and convincing speaker. He wrote prolifically in his spare time; and, while his health permitted, he seldom missed his week-end golf, to which he was devoted. In his latter years he found comfort and relaxation in his home life and the numerous attractions of his garden and farm in Sussex, together with regular changes to warm climates during the winter months. It is hard to realize that Blackham will be seen among us no more, but the man, his kindly nature, his wisdom, and his unfailing smile will survive in the minds of all those whose privilege it was to know and love him. To his devoted wife, in her great grief, the sympathy of all his many grateful friends and former colleagues is extended.

C. P. OLIVER, C.B., C.M.G., M.D.

Dr. C. P. Oliver, honorary physician to the King from 1913 to 1924, died at Maidstone on January 28, aged 89.

Charles Pye Oliver was born in 1861 at Hadlow. His father was a doctor who, like his son, was also well known in Maidstone, holding the office of mayor for a term. Charles Oliver studied medicine at Charing Cross and University College Hospitals, qualifying in 1885. He graduated M.B. in 1888, and proceeded M.D. in 1892. On qualification he set up in practice in Gabriel's Hill, Maidstone, and soon developed an

interest in public health, which led to his taking the D.P.H.(England) in 1896 and the examination in State medicine for the M.D. degree in 1903. In 1899 he was appointed medical officer of health for Maidstone, a post which he held for over 31 years. In addition to his general practice and public health duties he worked hard for the West Kent Hospital for many years, becoming senior physician in 1921. In his early days he used to visit patients on horseback.

Oliver had a long and distinguished career in voluntary military service. In 1887 he joined the Maidstone company of the Volunteer Medical Staff Corps, and was placed in command of field medical units. He represented the Maidstone Corps at Queen Victoria's funeral. When the Territorial Army was formed and the decision was made that women with nursing experience should be enrolled in Voluntary Aid Detachments, Oliver took an active part in enrolling recruits and became controller of V.A.D.s for Kent. In 1912 he was appointed A.D.M.S., Home Counties Division (T.A.), with the rank of colonel. He was a military member of the Territorial Army Association from its formation in 1908. His appointment as honorary surgeon to the King in 1913 was in recognition of his valuable services in field-ambulance work. On the outbreak of the first world war his first duty was to superintend the completion of the 2nd Eastern General Hospital at Brighton, which he had ready to function on August 23, 1914. He served in France for a time, and was A.D.M.S. of 67th Division. Later he was appointed A.D.M.S. to the Southern Army, and, in 1918, to the 23rd Army Corps. Three times mentioned in dispatches, he was appointed C.M.G. in 1918.

Many honours fell to Colonel Oliver on his return to civilian life. He was appointed a J.P. for Kent in 1920. From 1923–4 he was chairman of the Maidstone Division of the B.M.A., and he became president of the Kent Branch in the following year. In 1927 he was appointed C.B., and four years later Deputy Lieutenant of the county of Kent. Recently he had lived quietly in retirement, though he still played an active part in some local affairs. His wife died in 1919. He is survived by his four sons—one a doctor in Maidstone—and a daughter.

Dr. GUY WILLIAM PARRY died in Newport on December 31, 1950, at the comparatively early age of 62. He studied medicine at St. Bartholomew's Hospital, qualifying in 1914. After a period as house-physician and house-surgeon at the Bristol General Hospital he joined the R.A.M.C. and served with the Brigade of Guards in France, being awarded the *M.C.* Immediately after the war he acted as deputy commissioner to the Ministry of Pensions. He went into practice in Abergavenny in 1926, in partnership with Dr. H. L. S. Griffiths. He quickly established a very large country practice, and was on the staff of the Victoria Cottage Hospital. Besides being police surgeon, he was assistant county surgeon and an honorary life member of the Order of St. John of Jerusalem. A keen member of the B.M.A., he was chairman of the Monmouthshire Division from 1935–6 and a member of the Monmouth insurance and panel committees. After the establishment of the National Health Service he was appointed a member of the local executive council and of the hospital management committee. Dr. Parry was a man of many and varied interests who possessed a charming personality and who was equally at home in any society. He was a keen sportsman, and was at one time captain of the Monmouthshire Golf Club. He leaves a widow and two married daughters.—J. T. R.-E.

Medical Notes in Parliament

Gifts to Hospitals

Sir JOHN MELLOR asked the Minister of Health on February 1 if he would identify the powers by which he had instructed benefactors under covenant of voluntary hospitals to pay instalments to him; if he would publish a copy of his demand for such payment; and if he would refrain from enforcing such claims in the courts.

Mr. H. MARQUAND replied that the powers were contained in Section 7 of the National Health Service Act, 1946. He was advised that a person who executed a deed of covenant had himself no power to cancel it; and he hoped, therefore, that action in the courts to enforce compliance would not become necessary. The letter read:

Ref. A.G.D.5/Cov.
Dear Sir,

I have to communicate with you regarding the Deed of Covenant under which you covenanted on the to contribute the sum of £ for seven years to the above Hospital.

Under the provisions of the National Health Service Act, 1946, the sums formerly payable under such a Deed ceased to be payable to the Hospital concerned and became payable to the Minister of Health to be credited, with other hospital endowments, to the Hospital Endowments Fund, a fund set up under the Act.

The income from the Fund (including payments made under Covenants) is distributed to regional hospital boards and hospital management committees to be used by them as they think fit on hospital services such as, for example, the provision of amenities for patients and staff, or for medical and other research, beyond the provision made by the State.

In these circumstances I have to ask that you will be good enough to arrange for payments under the Deed entered into by you to be remitted annually to the Secretary, Ministry of Health, Whitehall, London, S.W.1, quoting the above reference number. Any payments which may have been made to the hospital since July 5, 1948, have already been credited to the Fund.

The remittances (whether made directly to this office or by means of a Banker's Order) should be made payable to the "Minister of Health Hospital Endowments Fund" and crossed "Bank of England."

Smallpox

On January 31 Mr. P. WELLS asked the Minister of Health (1) whether the nurses who volunteered to nurse at Bevendean Hospital during the smallpox outbreak at Brighton were vaccinated before they took up their duties; (2) on what date the staff of nurses, domestic workers, and others employed at Bevendean Hospital were vaccinated after the discovery of smallpox in the hospital; (3) how far the patients in Bevendean Hospital at the time of the discovery of smallpox in the hospital were sent home or to another hospital.

Mr. H. MARQUAND replied that no patients were sent home, but two who developed smallpox were sent to another hospital. The presence of smallpox in Bevendean was confirmed on December 28, and all staff employed there were vaccinated on that day or the next, except nine who were on leave and who were vaccinated on the 30th.

Mr. S. P. VIANT asked whether the Minister was aware that the removal of sufferers from smallpox from Bevendean Hospital to Dartford in very severe weather, with conditions of snow and ice, increased the risk of a fatal result, and what precautions would be taken to safeguard smallpox patients from such risk; which smallpox patients were nursed at Bevendean Infectious Diseases Hospital; why they were not sent to one of the other two isolation hospitals set apart for smallpox cases; whether there were patients suffering from other infectious diseases in Bevendean Hospital at the same time that smallpox cases were nursed there, after the outbreak was discovered; whether all the patients and staff at Bevendean Hospital were vaccinated as soon as smallpox was discovered there on December 28,

and on what dates the patients and staff at this hospital were vaccinated.

Mr. MARQUAND said that four persons suffering from smallpox were nursed at Bevendean. Two were transferred as soon as the diagnosis was made, two died before this was possible. Patients suffering from other infectious diseases were nursed there when the outbreak occurred; all were vaccinated on December 28 or 29, together with the staff, apart from nine staff on leave who were vaccinated on the 30th. There was no evidence that removal to Dartford caused any ill effects, but when the weather deteriorated a local hospital was also brought into use to avoid the longer journey.

Kingston Hospital Dispute

Mr. C. W. BLACK on January 30 raised the case of the Kingston and Malden Victoria Hospital. The proposals had been criticized strongly on many sides, and he hoped the Minister would agree to set up an independent inquiry, or at least not to close his mind on the issue, until a public petition was presented in the House.

Sir IAN FRASER said the situation was paralleled in Morecambe, where the Victoria Hospital was in the same plight. In 20 or 30 other towns the same situation existed.

Mr. FRED MESSER said that if the Minister conceded this he would have trouble from one end of the country to the other.

Mr. H. MARQUAND said the proposals of the regional board had not been drafted by the Labour Party. It was clear that a general problem was involved. The House had agreed on a National Health Service and on its regional organization. For that purpose regional boards were established to plan the hospital services so that in any region all specialties might be co-ordinated and provided in the most suitable way. Such reorganization was bound to affect some smaller hospitals. In every scheme such hospitals had to give up some specialties and become units for one specialty only, in order that one adequate unit might be available in every committee group. Consequently the functions of this particular hospital had to be changed. He was sure that the board did not make the change in any spirit of feeling that a general-practitioner hospital was undesirable. The regional board did not think that, the Ministry of Health did not think it, and his advisers did not think it. There was no animus against a general-practitioner hospital as such. In Kingston the regional board had found an outstanding need for a first-class gynaecological unit. The list of 300 women on the waiting-list could not be cut down until the scattered gynaecological facilities were centralized and improved.

In the area of the Kingston group there would be 226 beds under the new scheme compared with 203 at the moment, 102 maternity beds compared with 81, and 41 gynaecological beds compared with 37. Apart from the increase in beds there would be an increase in facilities. There could be no advantage in further inquiry. The Ministry knew all the facts and had to take action on them. Nevertheless, if Members liked to bring a deputation to meet him he would gladly explain the scheme more fully.

Universities and Colleges

UNIVERSITY OF LONDON

A course of two Special University Lectures will be delivered by Mr. S. R. M. Reynolds, Ph.D., Sc.D., of the Department of Embryology, Carnegie Institute of Washington, at St. Mary's Hospital Medical School (Wright-Fleming Institute Lecture Theatre), Paddington, London, W., on Wednesday and Thursday, February 14 and 15, at 5.30 p.m. His subject is "Uterine Accommodation of the Products of Conception." The lectures are addressed to students of the University and to others interested in the subject. Admission is free, without ticket.

Vital Statistics

Influenza

Influenza continues to be prevalent in the country as a whole, and the evidence is clear that it is due to virus A prime. In many areas attacked earlier the incidence is on the wane. In others, more newly attacked, it may not have reached the peak. The disease remains mild in type, and there is no indication that the experience of 1918–19 will be repeated.

In England and Wales during the week ending January 27 there was an increase in the number of deaths from influenza in the great towns, but the rate of increment remained low and was less than that for the preceding week. The death rate decreased in the Northern and North-western regions, though the latter still remained at the head of the list. Death rates increased in the North-midland, Midland, Eastern, and South-western regions and Wales, and there were slight rises in the East and West Ridings and London and South-eastern areas. In the Southern region there was a very slight fall. The rate per million of influenza deaths for England and Wales increased from 54 to 59.7.

Influenza deaths were mainly in the elderly, and more than 86% were over the age of 55 years. The number of pneumonia notifications increased in England and Wales and in the great towns, but the number of deaths decreased in the great towns. In London there was no significant change in the statistics of removals to hospital for influenza, pneumonia, and bronchitis in the week ending February 3.

Influenza is said to be prevalent in Yugoslavia—virus B. Influenza reported from Israel appears to be due to virus A prime. There is some influenza in Japan, but the type has not yet been identified.

The returns of deaths from influenza in the large towns for the week ending January 27 show that the mortality is declining in the areas where the outbreak first started but still rising in other areas. During the week the largest rise was in the Midland region, where the deaths numbered 213 compared with 108 in the preceding week.

The geographical distribution of influenza deaths is reflected in the incidence of general sickness. The new claims to sickness benefit under the National Insurance Act for the first four weeks of this year were as follows:

New Claims to Sickness Benefit (in Hundreds)

Region	Jan. 2	Jan. 9	Jan. 16	Jan. 23
Northern	281	363	240	176
East and West Riding	214	313	359	391
North-West	467	995	823	713
North-Midland	158	208	249	323
Midland	183	282	360	466
East	124	194	208	245
London and Middlesex	308	506	498	481
Remainder of S.E.	238	356	337	333
South	88	132	155	187
South-West	127	190	221	261
Wales	146	208	294	379
England and Wales	2,334	3,747	3,744	3,955
Scotland	128	416	525	426

In the great towns the following cases of and deaths from pneumonia, and deaths from influenza, have been reported:

	9/12	16/12	23/12	30/12	6/1	13/1	20/1	27/1
Pneumonia:								
Cases	347	374	364	502	956	1,300	1,455	1,720
Deaths	236	289	351	383	770	982	843	790
Influenza:								
Deaths	34	33	54	102	458	890	1,099	1,239

Totals from the first week of the year in the great towns compared with the preceding two years are as follows:

	1949	1950	1951
Pneumonia:			
Cases	2,212	2,174	5,413
Deaths	1,389	1,137	3,389
Influenza:			
Deaths	169	185	3,682

The following Table shows notifications of pneumonia—primary and influenzal—in England and Wales:

	9/12	16/12	23/12	30/12	6/1	13/1	20/1	27/1
Pneumonia ..	573	684	647	962	1,774	2,538	3,047	5,572
Corresponding week, 1949–50	734	676	634	842	1,120	991	890	902

The deaths cannot be related to the cases in these Tables.

Regional totals of influenza deaths in the great towns in the week ending January 27 and rates per million (in parentheses) were: Northern 34 (27.4), East and West Ridings 115 (49.2), North-western 379 (104.9), North Midland 76 (71.1), Midland 213 (92.7), Eastern 60 (79.8), London and South-eastern 216 (30.8), Southern 20 (76.8), South-western 74 (76.7), Wales 52 (78.4), all great towns 1,239 (59.7).

Influenza deaths in the great towns by age groups were: under 1, 2; 1–15, 6; 15–25, 8; 25–35, 13; 35–45, 32; 45–55, 90; 55–65, 202; 65–75, 402; 75 and over, 484; all ages, 1,239.

The following Table shows the great towns with the largest numbers of influenza and pneumonia deaths for the week ending January 27:

	Total Deaths	Deaths from (*a*) Influenza	Deaths from (*b*) Pneumonia	Deaths from (*a*) and (*b*)
Bradford ..	162	19	14	33
Leeds	286	26	35	61
Sheffield	232	19	11	30
Blackburn ..	116	19	10	29
Blackpool ..	111	25	11	36
Bolton	118	32	18	50
Liverpool ..	355	61	55	116
Manchester ..	388	72	48	120
Preston	98	18	10	28
Derby	94	14	11	25
Leicester	166	34	21	55
Nottingham ..	137	15	17	32
Birmingham ..	466	54	36	90
Coventry ..	93	20	9	29
Stoke-on-Trent ..	171	40	8	48
Walsall	96	36	3	39
Wolverhampton ..	102	26	6	32
Greater London ..	3,015	255	238	493
Norwich	72	16	6	22
Bristol	239	41	32	72
Swansea	87	24	4	28
Edinburgh ..	204	15	9	24
Glasgow	430	37	36	73
Belfast	214	35	33	68
Dublin	290	59	34	93

Poliomyelitis

In the week ending January 27 notifications of poliomyelitis were as follows: paralytic, 20 (29); non-paralytic, 7 (7); total, 27 (36). Figures for the previous week are in parentheses. Total notifications for the first four weeks of the years named are as follows: 1947, 42; 1948, 198; 1949, 106; 1950, 215; 1951, 148. The tendency for notifications in the current year to be lower than those in the other post-epidemic years is being maintained. Sixteen counties notified one case only apiece, and two counties two each. The remaining 7 cases were notified from Kent.

Week Ending January 27

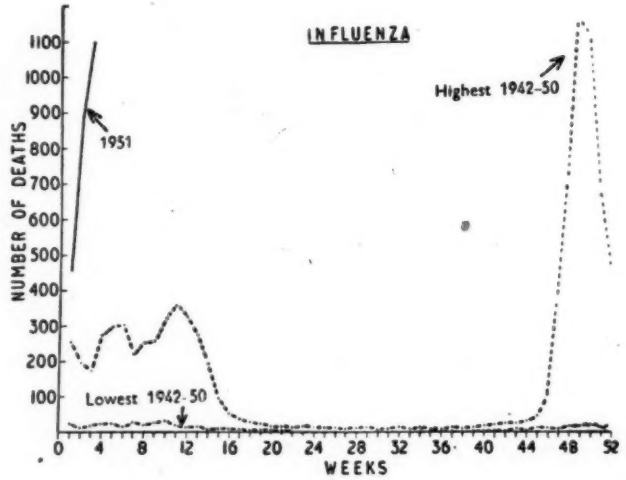
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 955, whooping-cough 5,023, diphtheria 48, measles 15,930, acute pneumonia 3,572, acute poliomyelitis 27, dysentery 706, smallpox 2, paratyphoid fever 4, typhoid fever 4. In the great towns 1,239 deaths were attributed to influenza.

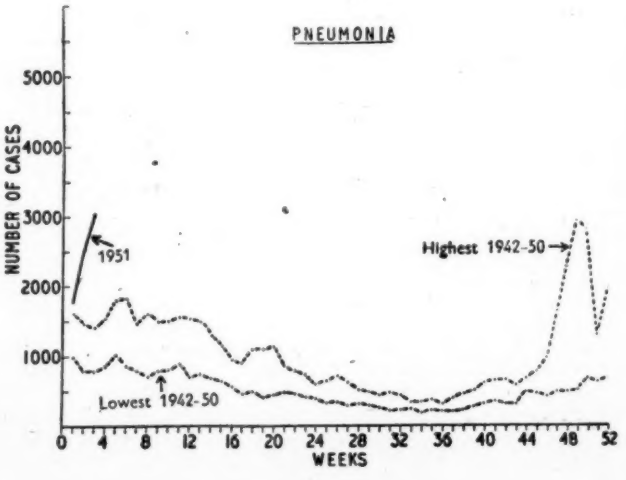
Infectious Diseases

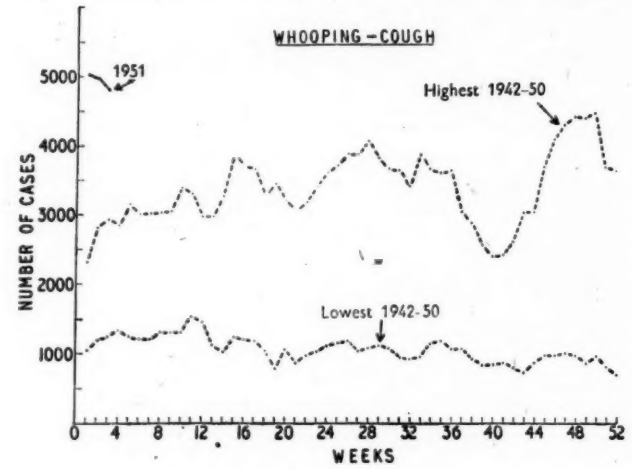
During the week ending January 20 the chief variations in the trends of infectious diseases in England and Wales were increases in the number of notifications of acute pneumonia 509, scarlet fever 157, and dysentery 29, and decreases for measles 2,679 and whooping-cough 169. The decline in the incidence of measles was general throughout the country, and nine counties reported falls of 100 or more in the number of notifications, the chief exceptions to the falling trend being Yorkshire North Riding and Dorset, with rises of 78 and 61 respectively. With the exception of a fall of 93 in Lancashire the variations in the trends of whooping-cough were small. The notifications of diphtheria increased by 12. The largest fluctuations in the trends of acute pneumonia were rises in Staffordshire 66, London 57, Warwickshire 51, Yorkshire West Riding 48, Glamorganshire 46, and a fall of 91 in Durham. The largest returns of acute poliomyelitis were Lancashire 6, Warwickshire 3 (all in Birmingham C.B.), Middlesex 3, Gloucestershire 3.

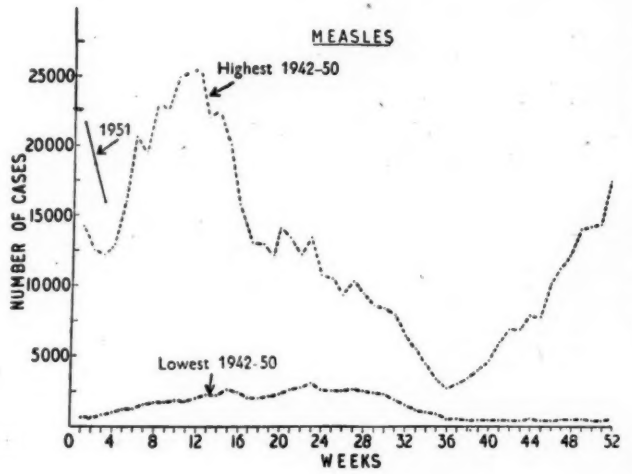
Graphs of Infectious Diseases

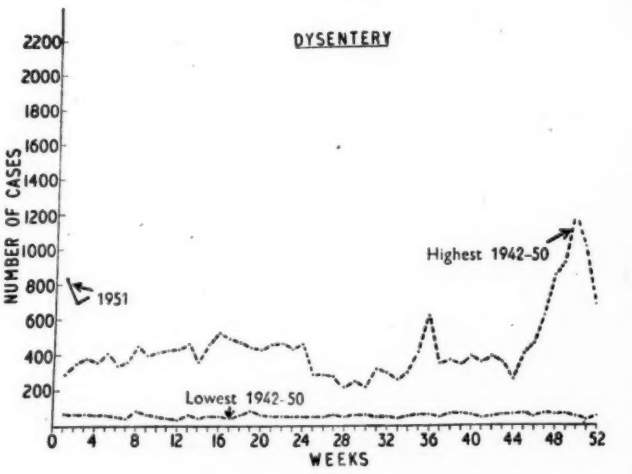
The graphs below show the uncorrected numbers of cases (deaths from influenza) of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus - - - - - - - -, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.











Dysentery

The high incidence of dysentery is still maintained. For the last 10 weeks this disease has been at the highest level recorded during recent years. The largest returns during the third week of the year were: London 86 (Finsbury 16, St. Marylebone 10); Leicestershire 76 (Leicester C.B. 59); Yorkshire West Riding 71 (Kirkburton M.B. 14, Saddleworth U.D. 10); Lancashire 61 (Oldham C.B. 19, Manchester C.B. 12); Staffordshire 57 (Lichfield R.D. 42); Middlesex 45 (Edmonton M.B. 12, Enfield U.D. 11); Sussex 42 (Brighton C.B. 22, Eastbourne C.B. 20); Southampton 40 (Bournemouth C.B. 32); Surrey 31 (Malden and Coombe M.B. 14); Northamptonshire 28 (Kettering M.B. 10, Brixworth R.D. 10); Shropshire 23 (Shrewsbury M.B. 14); Essex 20 (Ilford M.B. 12); Warwickshire 17 (Birmingham C.B. 11); Suffolk 15; Cheshire 15; Durham 13; Glamorganshire 12.

Tuberculosis

According to a statement issued by the Ministry of Health, deaths from tuberculosis have decreased sharply. Provisional figures for the first six months of 1950 show a drop of 17.7% as compared with the same period in 1949, when there was a drop of 5.6%. Deaths from respiratory tuberculosis fell by 1,671 (17.4%), compared with 247 (2.5%). The Ministry states that, though the returns must be interpreted with caution, much of the fall may be attributed to new methods of treatment, while increased services have also played a part. The number of new cases also declined. Provisional figures for 1950 fell by 5% (respiratory cases 4%). For several years past notifications of new cases had been increasing, and there had been a rise of 0.5% of respiratory cases in 1949 over 1948.

In the last six months of 1950, 761 new beds were provided and 386 reopened, a total of 1,147. Between the start of the Health Service in July, 1948, and June, 1950, 1,506 new beds were opened and 897 reopened, a total of 2,403. Thus 3,550 extra beds are in use, and more are promised.

London's Health

Provisional figures for 1950 issued by Sir Allen Daley, London County Council Medical Officer of Health, indicate that several records were broken last year, for the infant-mortality, neonatal-mortality, and maternal-mortality rates were lower than they have ever been before. These and some comparable figures are given in the table below.

Vital Statistics of London

	1931–40	1945	1946	1947	1948	1949	1950*
Infant mortality rate ..	60·0	44·0	38·0	34·0	31·0	27·0	25·0
Neonatal mortality rate	24·0	23·0	22·2	18·1	17·5	17·5	16·5
Maternal mortality rate	2·51	1·89	1·23	1·00	0·77	0·69	0·56
Birth rate	13·8	15·7	20·0	20·9	17·9	16·7	15·9
Death rate	12·7	14·1	12·6	12·5	11·1	11·7	11·3

* Figures for 1950 are provisional.

Before the war there were about 7,500 cases of diphtheria a year and 250 deaths; in 1950 there were just over 100 cases, with three deaths. Over 60% of infants under the age of 5 are immunized, and at school ages the percentage reaches 75. There were 60 deaths from infantile diarrhoea—the lowest number ever recorded. The incidence of whooping-cough was about average; the mortality was low—30 deaths. There were 3 deaths from scarlet fever and streptococcal sore throat, and 3 deaths from typhoid fever.

The annual notifications of cases of tuberculosis fell for the first time since the end of the last war (from 6,252 to 5,725). The provisional death rate for 1950 is 0.39 per 1,000—a new low record—compared with 0.52 in 1949. There were 1,300 deaths from tuberculosis in 1950.

Fatal road accidents caused 245 deaths; in 1949 there were 257.

Road Accidents

The provisional figure of road casualties for December, 1950, was 15,569. There were 355 deaths, as compared with 537 deaths in December, 1949, and 683 in December, 1938. The Ministry of Transport considers that the exceptionally heavy snow in December probably reduced the number of casualties by keeping people off the roads. The final figures for November, 1950, were: 510 killed, 4,380 seriously injured, 13,128 slightly injured, total 18,018. This is 3,235 more than in the corresponding month in 1949 and the highest total for any November since the war. The largest relative increase in casualties over November, 1949, was of motor-cyclists and their passengers.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the **week ending** January 20. (No. 3).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases: a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending January 20					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	42	2	9	2	4	74	7	30	5	1	991	478	74
Deaths	—	—	—	—	2	1	—	—	—	—			
Dysentery	727	86	132	1		177	25	52	—	—	377	131	72
Deaths		—		—					—				
Encephalitis, acute	3	—	—	—		4	—	—	1	—	4	1	—
Deaths		—			—		—			—			
Erysipelas			24	3	7			35	5	10			
Food-poisoning	66	5		—		35	11		—				
Infective enteritis or diarrhoea under 2 years				9	15					17			
Deaths	15		—	2	—	27		2	—	—			
Measles*	15,979	2,185	182	53	146	2,334	36	50	219	53	12,054	3,457	699
Deaths		2	—	—	1			—	—	—			
Meningococcal infection	44	7	33	3	1	45	4	19	—	—	132	62	34
Deaths		1	4				1	—					
Ophthalmia neonatorum	31	1	11	—		50	1	8	—	—	83	64	39
Pneumonia, influenzal	3,047	217	167	115	43	890	68	19	9	2	1,406	1,161	780
Deaths (from influenza)†	1,099	108	113	83	23	39	5	5	—	—			
Pneumonia, primary			590					328					
Deaths	843	118		60	37	233	36		14	18			
Poliomyelitis, acute:													
Paralytic	29	1	5	—	2	51	3	1	—	7	51	10	3
Non-paralytic	7	—											
Deaths§	3	—			—	3	—			—			
Puerperal fever			6				—	2					
Puerperal pyrexia‖	106	8	6	3	1	88	14	10	2	—	181	137	88
Scarlet fever	1,009	51	194	34	77	2,023	117	281	135	95	2,205	1,564	1,076
Deaths		1	—	—	—			—	—	—			
Smallpox	3	—	—	—		—	—	—	—	—			
Deaths				—					—	—			
(1) Tuberculosis, respiratory			145	31				186	33				
(2) Tuberculosis, non-respiratory			33	4				41	4				
(1) Deaths	249	37	35	18	13	200	29	38	7	16			
(2) Deaths		1	7	2	—		—	6	1	6			
Typhoid fever	4	—	—	—	1	5	—	—	—	3			
Deaths¶	—	—	—	—		—	—	—	—	—	17	8	4
Paratyphoid fever	2	—	5 (B)	—		1	—	—	—	—			
Whooping-cough	4,811	452	813	42	90	1,753	88	424	101	77	2,942	1,847	1,251
Deaths	8	1	4	—	1	4	2	—	—	—			
Deaths (0–1 year)	326	33	45	17	24	311	39	34	12	14	622	440	311
Deaths (excluding stillbirths)	9,868	1,511	1,240	425	375	5,282	828	653	125	226	6,868	5,881	5,222
Annual death rate (per 1,000 persons living)			24·9					13·1					
Live births	7,401	1,256	868	243	373	7,121	1,107	896	209	341	10,628	6,790	4,428
Annual rate per 1,000 persons living			17·4					18·0					
Stillbirths	190	26	23			178	25	19					
Rate per 1,000 total births (including stillborn)			26					21			291	230	178

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

Medical News

British Student Tuberculosis Fund

A letter in the *Journal* (December 30, 1950, p. 1497) opened the campaign to collect £50,000 to create a 100-bed centre and residential college for the treatment of students who have tuberculosis. It is thought that about 250 students a year would benefit from the combination of medical treatment with study, and it is the intention to spend about £14,000 on books, laboratory equipment, and staff—a full-time director of studies assisted by part-time tutors. The organizers point out that the centre will need only three nurses, whereas there are two nurses to every five patients in an ordinary sanatorium. The "Sanatoriums des Etudiants de France," on which the British scheme is to some extent modelled, opened its first sanatorium in 1933 and now disposes of over 700 beds—a further 460 being provided by associated organizations—in various institutions in France and Occupied Germany. Money is provided chiefly by local and national public authorities.

The British Fund is giving a concert on Friday, February 16, at 7.30 p.m., in the Royal Albert Hall, when Abbey Simon, Margaretta Scott, and the London Students' Orchestra, conducted by Boyd Neel, will give a programme of works by Tchaikowsky, Berlioz, Schubert, and other composers. Full details and tickets may be obtained from the Hall and the usual agents. The office of the Fund is Room 309, Tavistock House South, Tavistock Square, W.C.1.

Archives of the Middlesex Hospital

After a lapse of nearly 35 years the *Archives of the Middlesex Hospital* has resumed publication. The *Archives* first appeared in 1903, for the publication of papers from the Cancer Research Laboratories, and in 1905 was expanded in scope to include general clinical material. The first world war compelled the cessation of the *Archives* in 1916. The new *Archives* will appear quarterly, under the editorship of Dr. Douglas McAlpine. The first issue for January, 1951, includes papers on chronic mastitis, aortography, atypical abdominal tuberculosis, toxoplasmosis, diagnosis and treatment of cervical disk lesions, and reconstitution of the vas after vasoligation. The introduction is by Mr. Victor Bonney. The *Archives* is published by Messrs. E. and S. Livingstone, of Edinburgh, at a subscription of £2 2s. per annum.

French Medical Films

Twenty-five years ago there must have been few men of sufficient vision to foresee some of the surgical procedures of to-day. Operations half as extensive as are now practised on heart, lung, and brain would have been regarded by most as heroic or unjustifiable, possibly both. Such thought sprang naturally to mind at a showing of a series of sound and colour films presented by the Centre International du Film Médical at the Institut Français du Royaume Unis in London on January 30. *Patent Ductus Arteriosus*, by Professeur de Vernejoul, takes the viewer through the operation in animated diagrams of a novel type. The reflection of the muscular and aponeurotic layers is shown like the back drop of a stage being drawn up. The method, though bizarre, is clear and enhances the appreciation of the subsequent photography of an actual operation in progress. Some shots of the patient before and after the operation would have increased the value of the film to a general, as opposed to a specialized, medical audience. The same criticism applies to the film shown on *Glosso-Pharyngo-Laryngectomy*, by Professeur Portmann, of the Académie de Médecine, and on *Prefrontal Leucotomy*, by Professeurs Wertheimer and Dechaume, of Lyons. Both these films are clear expositions of the operation. Another interesting film shown was by Professeur Santy on splenectomy and portal-renal anastomosis in the *Surgical Treatment of Portal Hypertensions*. The remaining film was entitled *Functional Liberation of the Lung*, by Drs. Warnery and Metras, of the Sanatorium du Petit Arbois. In this some of the *x*-ray photographs demonstrating the effect of the operation are difficult to interpret, but the steps of the operation are excellently filmed.

The colour and photography in all these films are good. The films are technically interesting and valuable. The almost casual manner in which the routine dusting of the operation field with sulphonamide and penicillin powder was done seemed a significant reminder of how these discoveries have made such surgery safe for the patient.

Leverhulme Research Fellowships

Application is invited for Leverhulme fellowships and grants in aid of research. They are intended for senior workers prevented by routine duties or pressure of other work from carrying out research. They are limited to British-born subjects normally resident in the United Kingdom; in exceptional circumstances the trustees may waive the condition as to residence. The trustees will also consider applications from groups of workers engaged on co-operative programmes of research, particularly from those engaged on long-term programmes. The duration of the awards will not normally extend over more than two years or less than three months, and the amount will depend on the nature of the research and the circumstances of the applicant. Forms of application may be obtained from the secretary, Lord Haden-Guest, Leverhulme Research Fellowships, 3–5, Salisbury Square, London, E.C.4. Applications must be received on or before March 1. Awards will be announced in July and will date from September 1, 1951.

Elliston Scholarships

The London School of Hygiene is offering two special scholarships for the 1951 course for the Diploma in Public Health. See the letter on page 302, and our advertisement columns.

Montana Hall for Sale

Montana Hall, the British-built, British-staffed, eighty-bed modern tuberculosis clinic for British patients in Switzerland, is up for sale because it is no longer getting patients from Britain in sufficient number. It is said that the running cost per patient is in the region of £2 a day when the hospital is full, and, since the National Health Service has no legal right to send tuberculous patients there, only those paying their own fees have made use of the facilities.

In Brief

At the annual general meeting of the British Association of Otolaryngologists on December 1, Mr. V. E. Negus was elected president, Professor F. C. Ormerod vice-president, Mr. F. C. W. Capps secretary, and Mr. W. A. Mill treasurer for the season 1950–1.

COMING EVENTS

Medical Jargon

The next meeting of the Medical Section of the Library Association will take place at 11, Chandos Street, London, W.1, on Friday, February 16, at 7 p.m., when Dr. W. R. Bett will speak on "Problems of Medical Language and Jargon." The meeting is open to all.

Thirteenth British Congress of Obstetrics and Gynaecology

The Congress will be held at Leeds, Yorkshire, on July 8–11, 1952. The subjects for discussion are abnormal uterine action in labour, stress incontinence of urine, the place of the paediatrician in a maternity unit, and genital tuberculosis in the female. All communications relating to this congress should be addressed to the secretary, Mr. B. L. Jeaffreson, 32, Park Square, Leeds, 1.

Cash Prize Award Contest

The National Gastroenterological Association will award $100 and a certificate of merit in September for the best unpublished contribution on gastro-enterology or allied subjects. All entries for the 1951 prize should be limited to 5,000 words, be typewritten in English, prepared in manuscript form, submitted in five copies accompanied by an entry letter, and must be received not later than June 1. Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. The decision of the judges will be final, and the association reserves the exclusive right of publishing the winning contribution, and those receiving certificates of merit, in its official publication, *The Review of Gastroenterology*. Entries should be addressed to the National Gastroenterological Association, 1819, Broadway, New York, 23, N.Y.

Medical Courses in Paris

The following courses will be held at the Broussais Hospital, Paris: Renal pathology, from April 21 to 26, the number of entries being limited and the fee 3,000 francs; full particulars may be obtained from Dr. René Wolfromm, Clinique Médicale Propédeutique, Hôpital Broussais, 96, rue Didot, Paris, 14e; "Journées Médicales Annuelles," on recent developments in medicine, on April 27, 28, and 29, the participants limited to 150, and the registration fee 2,000 francs; further information from Professor Jean Hamburger, 29, Boulevard de Courcelles, Paris, 8e; and allergic diseases, from April 30 to May 5, without charge, except for those taking part in the practical demonstrations, the fee for which is 3,000 francs. Full particulars may be had from the secretary of the Clinique Médicale Propédeutique.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

●INSTITUTE OF CHILD HEALTH, Hospital for Sick Children, Great Ormond Street, London, W.C.—February 12, 5 p.m., "*Variations in Infective Diseases*," by Dr. H. S. Banks.

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, Cavendish Square, London, W.—February 12, 8.30 p.m., discussion: "*Recent Advances in the Treatment of Carcinoma of the Breast*," to be introduced by Mr. H. J. B. Atkins and Mr. J. Ralston K. Paterson.

SCOTTISH SOCIETY OF THE HISTORY OF MEDICINE.—At Royal Faculty of Physicians and Surgeons of Glasgow, 242, St. Vincent Street, Glasgow, February 12, 4.30 p.m., "*John Reissberg Wolfe, 1823–1904*," paper by Professor W. J. Brownlow Riddell; "*The Puzzle of Peter Lowe*," short communication by Mr. A. L. Goodall.

Tuesday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., February 13, 5.30 p.m., "*The Antithyroid Drugs*," by Dr. Russell Fraser.

CHELSEA CLINICAL SOCIETY.—At South Kensington Hotel, 47, Queens Gate Terrace, London, S.W., February 13, 7 for 7.30 p.m., discussion: "*The Impact of Politics on Medicine*," to be opened by Dr. S. Wand, followed by Mr. Lawrence Abel and Dr. J. A. Gorsky.

INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—February 13, 5 p.m., "*Pathology*," by Dr. J. O. Oliver.

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, London, W.C.—February 13, 5 p.m., "*The Psychopathology of Cerebral Diseases*," by Professor Manfred Bleuler (University of Zurich).

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—February 13, 5.30 p.m., "*Nervous Aspects of the Control of the Intra-ocular Pressure*," by Dr. Hugh Davson.

LONDON UNIVERSITY.—At Westminster Medical School (Meyerstein Lecture Theatre), Horseferry Road, London, S.W., February 13, 5 p.m., "*The Adrenocorticotrophic Hormone of the Pituitary Gland*," by Mr. C. J. O. R. Morris, Ph.D., M.Sc.

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.—February 13, 5 p.m., "*Leptospirosis*," Milroy Lecture by Dr. J. C. Broom. (See also February 15.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—February 13, 5 p.m., "*Tumours of the Orbit*," Hunterian Lecture by Professor Harvey Jackson.

Wednesday

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—February 14, 5 p.m., "*Medical Mycology*," lecture-demonstration by Dr. R. W. Riddell.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—February 14, 2.45 p.m., "*Acromegaly and Acromegaloid States: Psychiatric and Genetic Aspects*," by Professor Manfred Bleuler (University of Zurich).

LONDON UNIVERSITY.—At St. Mary's Hospital Medical School (Wright-Fleming Institute Lecture Theatre), Paddington, London, W., February 14, 5.30 p.m., "*Uterine Accommodation of the Products of Conception*," by Mr. S. R. M. Reynolds, Ph.D., Sc.D. (Carnegie Institute of Washington). (See also February 15.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—February 14, 5 p.m., "*The Hunterian Heritage*," Hunterian Oration by Sir Max Page.

ROYAL SANITARY INSTITUTE, 90, Buckingham Palace Road, London, S.W.—February 14, 2.30 p.m., discussions: "*The Problem of Reduction of Atmospheric Pollution*," to be opened by S. R. Craxford, D.Phil., B.A., and W. J. Sparkes, B.Sc., A.M.I.Mech.E.; "*The Measurement and Survey of Atmospheric Pollution*," to be opened by S. H. Richards, M.Sc.

●ROYAL SOCIETY OF ARTS, John Adam Street, Adelphi, London, W.C.—February 14, 2.30 p.m., "*1851–1951: A Century of British Science*," by Mr. D. McKie, D.Sc., Ph.D.

Thursday

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, London, W.—February 15, 8.15 p.m., "*The Relative Value of Radiology in the Prevention of Tuberculosis*," by Dr. J. F. Brailsford.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., February 15, 5.30 p.m., "*Neural Control of the Pituitary Gland*," by Dr. G. W. Harris.

CHARING CROSS HOSPITAL MEDICAL SCHOOL, Chandos Place, London, W.C.—February 15, 6 p.m., "*T. H. Huxley, Humanist*," Biennial Huxley Lecture by Lord Horder.

EDINBURGH CLINICAL CLUB.—At B.M.A. Rooms, 7, Drumsheugh Gardens, Edinburgh, February 15, 8 p.m., "*Osteoarthritis*," by Mr. G. A. Pollock.

●HUNTERIAN SOCIETY.—At Claridge's, Brook Street, London, W., February 15, 7 for 7.30 p.m., annual dinner.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—February 15, 5.30 p.m., "*Physiological Factors Affecting the Penetration of Antibiotics into the Eye*," by Dr. M. Langham.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—February 15, 3 p.m., "*Experimental Psychoses and Other Abnormal Mental States Produced by Drugs*," by Dr. W. Mayer-Gross.

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool.—February 15, 8 p.m., "*The Present Scope and Limitations of Radiotherapy*," by Dr. J. S. Fulton.

LONDON UNIVERSITY.—At St. Mary's Hospital Medical School (Wright-Fleming Institute Lecture Theatre), Paddington, London, W., February 15, 5.30 p.m., "*Uterine Accommodation of the Products of Conception*," by Mr. S. R. M. Reynolds, Ph.D., Sc.D. (Carnegie Institute of Washington). (See also February 14.)

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.—February 15, 5 p.m., "*Leptospirosis*," Milroy Lecture by Dr. J. C. Broom. (See also February 13.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—February 15, 5 p.m., "*Congenital Deformities of Mechanical Origin, their Pathology and Treatment*," Hunterian Lecture by Professor Denis Browne.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At 26, Portland Place, London, W., February 15, 7.30 p.m., "*Recent Investigation into the Treatment of Schistosomiasis by Miracil D in Egypt*," by Dr. J. Newsome.

ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Materia Medica Department, Medical School, Small's Wynd, Dundee, February 15, 5 p.m., "*The Family Doctor and the Future*," by Dr. George MacFeat.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—February 15, 4.30 p.m., lecture-demonstration on neurology.

UNIVERSITY COLLEGE (Anatomy Theatre), Gower Street, London, W.C.—February 15, 1.15 p.m., "*Population Trends*," by Mr. W. J. Corlett.

WESTMINSTER SCHOOL OF MEDICINE, Meyerstein Lecture Theatre, Horseferry Road, London, S.W.—February 15, 5 p.m., clinico-pathological demonstration. Discussion: "*Post-operative Pulmonary Collapse*," by Dr. R. D. Tonkin.

Friday

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, London, W.—February 16, 5 p.m., meeting of medical members.

EUGENICS SOCIETY.—At 26, Portland Place, London, W., February 16, 5 p.m., "*Eugenics and Human Oecology*," the Galton Lecture by G. C. L. Bertram, M.A., Ph.D.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., February 16, 2.15 p.m., Diagnosis Section Meeting. Paper: *"Behaviour of Lipiodol in the Bronchial Tree,"* by Dr. C. J. Hodson; film: *"Radiological Studies of Movements of the Duodenal Cap, Duodenum, and Jejunum in Man,"* by Drs. J. W. McLaren and G. M. Ardran. Presented by Dr. Ardran.

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—February 16, 8 p.m., *"What is a Hospital For?"* address by Professor J. M. Macintosh.

Saturday

BIOCHEMICAL SOCIETY.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., February 17, 11 a.m., 294th meeting. Symposium: *"The Biochemistry of Fertilization and the Gametes."*

CAMBRIDGE UNIVERSITY.—At Girton College, February 17, 5.15 p.m., *"The Doctor's Dilemma,"* Founders' Memorial Lecture by Lord Moran.

APPOINTMENTS

Dr. H. K. Snell has been appointed Inspector of Retreats under the Inebriates Acts, 1879 to 1898.

LEMIN, MAURICE EVAN, M.B., Ch.B., Deputy School Medical Officer, Birmingham Education Committee.

LOCKHART, ROBERT, M.B., Ch.B., D.P.H., Medical Officer, British Aluminium Co., Ltd. (Scottish Works).

REID, REGINALD DOUGLASS, M.B., B.S., D.T.M.&H., Morbid Histologist (Consultant) Colchester (North-east Metropolitan Regional Hospital Board).

SHEFFIELD REGIONAL HOSPITAL BOARD.—The following whole-time consultant appointments are announced: *Psychiatrist at Carlton Hayes Hospital, Narborough*, Sylvia M. FitzG. Reid, M.B., B.Ch., D.P.M. *Child Psychiatrist at Towers Hospital, Leicester*, A. K. Graf, M.D. *Chest Physician to Leicester Area*, M. C. Brough, M.D. *Psychiatrist to Saxondale Hospital, Radcliffe-on-Trent*, A. D. McL. Douglas, M.B., Ch.B., D.P.H.

TAYLOR, GORDON CUNNINGHAM, M.B., Ch.B., D.P.H., Assistant Senior Medical Officer, South-west Metropolitan Regional Hospital Board.

THOMPSON, HENRY WORSLEY, M.B., Ch.B., Visiting Medical Officer, Rossall Hospital, near Fleetwood, Lancs.

WALKER, SARAH, M.D., D.P.H., Chief Assistant Medical Officer, Maternity and Child Welfare, Bristol.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Gilmour.—On January 28, 1951, at Hayes, Middlesex, to Jean, wife of Dr. S. J. G. Gilmour, a son.

Hancock.—On January 24, 1951, at Middlesex Hospital, to Vera (formerly Thomas), wife of Dr. Ronald E. Hancock, a son—Paul Byron.

Inglis.—On January 11, 1951, at Queen Elizabeth Hospital, Birmingham, to Irene, wife of James McNaught Inglis, M.B., Ch.B., D.A., a sister for Timothy. (Premature.)

McAleer.—On January 24, 1951, at Hornchurch, Essex, to Maureen, wife of Thomas Burke McAleer, M.B., Ch.B., a son—Michael John.

McMillan.—On January 29, 1951, at Chertsey Hill Nursing Home, to Dr. and Mrs. R. L. McMillan, Whiteclosegate, Carlisle, a son.

Ring.—On February 2, 1951, to Dr. Stella Ring, wife of Mr. Peter Ring, F.R.C.S., a son.

Seymour-Jones.—On January 20, 1951, at Yarborough Nursing Home, Southsea, to Elizabeth (formerly Pinches), wife of Anthony Seymour-Jones, F.R.C.S., a daughter—Mary Louise.

Tibbetts.—On January 29, 1951, at Birmingham, to Doreen, wife of Dr. R. W. Tibbetts, a daughter.

Walwyn-Jones.—On January 23, 1951, to Margaret (formerly Pemberton), wife of Dr. E. O. Walwyn-Jones, 88, Sussex Gardens, London, W., a daughter.

DEATHS

Bannister.—On January 29, 1951, at his home, 47, Grove Way, Esher, Surrey, William Jacob Bannister, M.D., D.P.H., aged 73.

Bean.—On January 23, 1951, at 257, Leeds Road, Ilkley, Yorks, Walter Percy Bean, L.S.A., aged 82.

Brown.—On January 18, 1951, at Spencer Cottage, Minchinhampton, near Stroud, Glos, Alfred Brown, M.D., late of Highcroft, Minchinhampton, aged 72.

Buchanan.—On January 22, 1951, at Newark, Notts, Robert Buchanan, M.B., C.M., D.P.H., late of Broughty Ferry, Forfarshire, aged 83.

Chapman.—On January 21, 1951, at 46, Fairacres, Roehampton Lane, London, S.W., Charles Leopold Granville Chapman, F.R.C.S.I., late of Grimsby, aged 74.

Fielding-Ould.—On January 18, 1951, at 29, Norfolk Crescent, London, W., Robert Fielding-Ould, M.D., M.R.C.P.

Hastings.—On January 20, 1951, at Edinburgh, Harry Hastings, O.B.E., M.B., Ch.B., D.T.M.&H., of Calabar, Nigeria, W. Africa, and 149, Warrender Park Road, Edinburgh.

Hector.—On January 21, 1951, at Foresterhill, Aberdeen, Mabel Hector, M.B., Ch.B. of Runrigs, Pitfodels, Aberdeenshire, late of the Dow Memorial Hospital, Gujrat, Punjab, India.

Lamb.—On January 20, 1951, at his home, Dibden, Purlieu, Southampton, John Henry Lamb, M.B., Ch.B., late of Bishop's Castle, Salop.

Mackenzie.—On January 26, 1951, Marion Ellen Mackenzie, M.B., Ch.B., of Headingley, Leeds.

McLeish.—On January 20, 1951, at 94, Hillway, Highgate, London, N., Roberta McLeish, M.B., Ch.B.

Scudamore.—On January 22, 1951, at Bournemouth, Charles Edward Scudamore, L.R.C.P., aged 92.

Thompson.—On January 25, 1951, at 170, Heaton Moor Road, Stockport, Charles Herbert Thompson, M.B., B.Ch.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Whooping-cough Quarantine and Immunity after Treatment with Chloramphenicol

Q.—*With the advent of chloramphenicol for the treatment of whooping-cough, I should be grateful if you could tell me (1) whether there should be any alteration in the quarantine period following an apparently successful course of treatment, and (2) whether such a successfully treated attack confers the same degree of immunity on the patient as an untreated attack.*

A.—(1) While it is true that the successful clinical treatment of infections with the modern antibiotics is usually accompanied by bacteriological cure—that is, elimination of the infecting organism—a notable exception is the persistence of the typhoid bacillus in the faeces of cases of typhoid fever successfully treated with chloramphenicol. It is too early yet to say whether this drug is effective in eliminating *H. pertussis* in treated cases of whooping-cough, although there is some (unpublished) evidence that the organism may persist in the respiratory tract during treatment. The period of quarantine in whooping-cough is usually given as six weeks, but in most cases, whether treated or not with antibiotics, the organism cannot be demonstrated in cough plates or post-nasal swabs after the fourth to fifth week.

(2) Antibodies against *H. pertussis* develop rather late, from the third week onwards, and again it is too early to say whether chloramphenicol will interfere to any extent with the development of immunity. Relapses have been common in other continued fevers like typhoid and typhus, and it is possible that in cases of whooping-cough treated early in the infection there may be some interference with the development of protective antibody.

Lipoid Pneumonia

Q.—*What are the diagnostic features of lipoid pneumonia, as compared with other forms of pneumonia? Does lipoid pneumonia ever occur in adults or adolescents? What are the prognosis and treatment?*

A.—The diagnosis of "lipoid pneumonia" is difficult. The term is usually used to denote a pneumonia caused by aspiration of oil into the respiratory tract. This may be mineral oil (liquid paraffin) or animal oil such as cod-liver oil, or more rarely vegetable oils taken as food. It is important to note, however, that fatty change can occur in chronic pneumonic processes, such as those which constitute one form of pulmonary suppuration, and those occurring beyond bronchial obstruction—for example, by a carcinoma. Hence, to substantiate a diagnosis of oil-aspiration pneumonia the finding of lipoid material in histological sections of the lung is not sufficient; the oil must be proved to be exogenous by appropriate chemical or micro-chemical tests. Clinically the diagnosis of lipoid pneumonia is extremely difficult. There is one group of cases which occurs in feeble infants to whom cod-liver oil or liquid paraffin has been administered. In these the illness presents as a low-grade bronchopneumonia, generally complicating some preceding illness, and the diagnosis is almost impossible to make clinically. The other group occurs in adults generally of middle age or over. There is usually a history of long-continued use of mineral oil as a nasal application in drops or by spray; sometimes the condition appears to follow the long-continued use of mineral oil by mouth, but in these cases there is often a history of dysphagia or of laryngeal lesions. A few cases of oil-aspiration pneumonia have been reported in patients with achalasia of the cardia who

have used mercury bougies lubricated with liquid paraffin; the liquid paraffin floats on top of the stagnant contents of the dilated oesophagus and readily spills over into the bronchopulmonary tree. In these adult cases oil-aspiration pneumonia produces very few symptoms, and is often found only as a result of radiographic examination, when shadows, which may be either localized or diffuse, are seen. A few cases have been reported in which a so-called "paraffinoma" has caused a localized shadow in the lungs suggesting a carcinoma and has led to surgical resection of the affected lobe or lung. In such cases the procedure leading up to the aspiration of oil has presumably been carried out by the patient customarily in one position so that the same bronchopulmonary segment receives the aspirated oil on every occasion.

Treatment is entirely prophylactic, since the established lung lesion is quite unaffected by any form of medical treatment. Oily preparations should not be used in the nose, mineral oil should not be taken by patients with any form of dysphagia, and great caution should be exercised in the administration of oily preparations of all sorts to infants.

Cold-agglutinin Titres in Atypical Pneumonia

Q.—*What titre of cold agglutinins is diagnostic in atypical pneumonia?*

A.—A considerable number of the clinically and radiologically acceptable cases of primary atypical pneumonia of uncertain aetiology do not develop any antibody either of the cold-agglutinin type or against the non-haemolytic streptococcus MG. These antibodies usually appear in the more severe cases from the seventh to tenth day of infection. Using a 1% suspension of red blood cells and reading the results macroscopically after overnight incubation at 4° C., a positive cold-agglutinin reaction in a dilution of 1:32 of the patient's serum is usually regarded as diagnostic. If it is possible to take two samples of blood, the first as early as possible and the second 10–14 days after onset, a two- to four-fold rise in titre is also probably diagnostic. Cold agglutinins may develop in other diseases—for example, cirrhosis of the liver, haemolytic and Addison's anaemia, septicaemia—and following sulphonamide therapy, but trypanosomiasis is the only infection in which a high titre may be found. In a group of 132 patients with a variety of respiratory infections other than atypical pneumonia, only five had a cold-agglutinin titre exceeding 1:16 (*Lancet*, 1943, 1. 765).

Aqueous Tinctures

Q.—*I have been my own dispenser for about 38 years, and have always bought aqueous tinctures for cheapness, having been assured by my drug firm that such are the same as Pharmacopoeial tinctures, except of course for glycerin and water taking the place of spirit. My local chemist tells me that aqueous tinctures are deplorable and must lack many constituents only soluble in alcohol. In fact he labels them "cheap and nasty." What is your opinion?*

A.—The chemist is right. A tincture implies an alcoholic extract made up in various dilutions. The so-called aqueous tinctures, in which glycerin and water are substituted for alcohol, came into popularity during the war on account of the scarcity of alcohol. They are no real substitute for genuine tinctures, as the solvents used do not by any means always abstract the active principle satisfactorily.

Streptomycin in Tuberculous Meningitis

Q.—*What are the indications for discontinuing intrathecal and systemic streptomycin in tuberculous meningitis?*

A.—There are no standardized indications for discontinuing the administration of intrathecal and systemic streptomycin in tuberculous meningitis. At some hospitals streptomycin treatment is stopped when the C.S.F. has returned to normal—for example, when the sugar content is normal and the number of cells is less than 5 per c.mm. On the other hand, there is at least one hospital where 2 g. of streptomycin is given intramuscularly (in divided doses) and 100 mg. intrathecally daily for six months, except on one day in seven after the first month, irrespective of improvement in the clinical condition or the C.S.F. findings. The development of dermatitis, deafness, or vestibular disturbance must not be allowed to interrupt the course of streptomycin therapy.

Allergic to Cats

Q.—*A woman is allergic to cats, but her symptoms are usually only of a minor nature. Recently, however, when complicated by influenza, her allergic reaction took the form of a severe attack of asthma. What treatment is advised?*

A.—Allergic sensitivity is often intensified by an infection. Vigorous symptomatic treatment will in these cases often be followed by a return to the previous level of sensitivity. Desensitization to cat hair is reasonably effective provided an extract is obtained which, on testing gives a well-marked skin reaction. A number of pharmaceutical firms put up extracts, and will supply details of dosage. If the symptoms persist it is probably more effective, and certainly less tedious, to abolish the cat rather than to attempt desensitization, which is often only partially successful and may be transient.

Significance of an Epileptic Aura

Q.—*A professional woman of 28 was subject to psychomotor attacks throughout her childhood: she would experience for a few seconds a peculiar epigastric sensation, during which period she would continue whatever she was doing at the time, but could not speak or answer questions. When she was 22 this type of attack was followed by her first bout of petit mal, and since then she has had four or five attacks of petit mal, usually preceded by the aura mentioned above. Her last attack of petit mal was 11 months ago, and since then she has had four aurae without subsequent petit mal. She gives a history of having been a difficult breech delivery. There is no family history of the complaint. E.E.G. facilities are not available at her overseas station. She desires to marry only when she has been free from such attacks for a period of two to three years, being under the impression that that interval may be taken as a test of cure. What advice should be given to her?*

A.—The description of the present attacks is incomplete, but the presence of an epigastric aura makes it fairly certain that they do not belong to the group for which troxidone is of specific value (see *Journal*, November 4, 1950, p. 1047). It is not uncommon for the aura to occur alone; this in fact represents a minimal epileptic seizure. In view of the total length of the history, freedom from attacks for a period of two or three years would be no guarantee against their recurrence, though the longer the period of freedom the greater the hope of non-recurrence. If the liability is inherited, waiting cannot make any difference to the risk of transmission to offspring. If, however, the partner were free from epileptic attacks, with a normal E.E.G. and a negative family history for epilepsy, the chances of offspring being afflicted with epilepsy are practically negligible. In view of the age of onset and type of attack it is probable that the liability in this case is inborn rather than acquired.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
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